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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 September 2013 (26.09.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/138860 A1

(51) International Patent Classification:
C07D 417/14 (2006.01) *A61P 31/04* (2006.01)
C07D 417/02 (2006.01) *A61K 31/428* (2006.01)
A61K 31/429 (2006.01)

(21) International Application Number:
PCT/AU2013/000286

(22) International Filing Date:
21 March 2013 (21.03.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/614,044 22 March 2012 (22.03.2012) US

(71) Applicant: **BIOTA EUROPE LIMITED** [GB/GB]; Begbroke Business & Science Park, Sandy Lane, Yarnton, Oxfordshire OX5 1PF (GB).

(72) Inventor; and
(71) Applicant *(for MG only)*: **LUNNISS, Christopher James** [GB/AU]; c/- Biota Scientific Management Pty Ltd, 10/585 Blackburn Road, Notting Hill, Victoria 3168 (AU).

(72) Inventors: **PALMER, James T**; c/- Biota Scientific Management Pty Ltd, 10/585 Blackburn Road, Notting Hill, Victoria 3168 (AU). **PITT, Gary Robert William**; c/- Biota Scientific Management Pty Ltd, 10/585 Blackburn Road, Notting Hill, Victoria 3168 (AU). **AXFORD, Lorraine Claire**; c/-Biota Scientific Management Pty Ltd, 10/585 Blackburn Road, Notting Hill, Victoria 3168 (AU). **DAVIES, David**; c/- Biota Europe Limited, Begbroke Business and Science Park, Sandy Lane, Yarnton Oxfordshire OX5 1PF (GB).

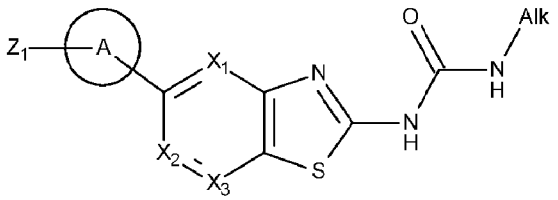
(74) Agent: **FB RICE**; Level 23, 200 Queen Street, Melbourne, Victoria 3000 (AU).

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

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

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: ANTIBACTERIAL COMPOUNDS



(I)

(57) Abstract: The present invention provides a compound of the following formula, salts, racemates, diastereomers, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof. Also provided is the use of these compounds as anti-bacterials, compositons comprising them and processes for their mancfacture.

WO 2013/138860 A1

ANTIBACTERIAL COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to a novel class of compounds, their use as antibacterials, compositions comprising them and processes for their manufacture.

BACKGROUND

Type II topoisomerases catalyse the interconversion of DNA topoisomers by transporting one DNA segment through another. Bacteria encode two type II topoisomerase enzymes, DNA gyrase and DNA topoisomerase IV. Gyrase controls DNA supercoiling and relieves topological stress. Topoisomerase IV decatenates daughter chromosomes following replication and can also relax supercoiled DNA. Bacterial type II topoisomerases form a heterotetrameric complex composed of two subunits. Gyrase forms an A_2B_2 complex comprised of GyrA and GyrB whereas topoisomerase forms a C_2E_2 complex comprised of ParC and ParE. In contrast eukaryotic type II topoisomerases are homodimers. Ideally, an antibiotic based on the inhibition of bacterial type II topoisomerases would be selective for the bacterial enzymes and be relatively inactive against the eukaryotic type II isomerases.

The type II topoisomerases are highly conserved enzymes allowing the design of broad-spectrum inhibitors. Furthermore, the GyrB and ParE subunits are functionally similar, having an ATPase domain in the N-terminal domain and a C-terminal domain that interacts with the other subunit (GyrA and ParC respectively) and the DNA. The conservation between the gyrase and topoisomerase IV active sites suggests that inhibitors of the sites might simultaneously target both type II topoisomerases. Such dual-targeting inhibitors are attractive because they have the potential to reduce the development of target-based resistance.

Type II topoisomerases are the target of a number of antibacterial agents. The most prominent of these agents are the quinolones. The original quinolone antibiotics included nalidixic acid, cinoxacin and oxolinic acid. The addition of fluorine yielded a new class of drugs, the fluoroquinolones, which have a broader antimicrobial spectrum and improved pharmacokinetic properties. The fluoroquinolones include norfloxacin, ciprofloxacin, and fourth generation quinolones gatifloxacin and moxifloxacin. The coumarins and the cyclothialidines are further classes of antibiotics that inhibit type II topoisomerases, however they are not widely used because of poor permeability in bacteria, eukaryotic toxicity, and low water solubility.

Examples of such antibiotics include novobiocin and coumermycin A1, cyclothialidine, cinodine, and clerocidin.

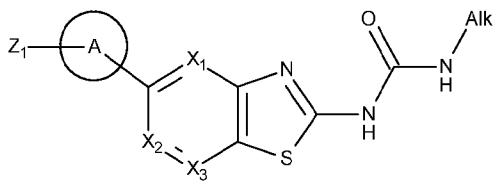
Linezolid is currently the standard treatment for acute bacterial skin and skin structure infections (ABSSSI) caused by Gram-positive bacteria. It belongs to the class of oxazolidinones and is a protein synthesis inhibitor.

However, the continual emergence of antibiotic resistance demands that novel classes of antibiotics continue to be developed and alternative compounds that inhibit bacterial topoisomerases are required.

WO2007/148093, WO2009/074812, WO2009/074810 and WO2012/045124 describe the applicant's earlier compounds that inhibit bacterial gyrase activity. The applicant has now discovered a class of related compounds that includes a carbocyclic or heterocyclic ring comprising a branched i.e. secondary or tertiary alcohol substituent and prodrugs thereof which appears to confer advantage(s) to the compounds. One or more advantage(s) include desirable pharmacokinetic properties, prodrugability, solubility and introduced chirality to provide a further subclass of active enantiomers.

SUMMARY

According to a first aspect there is provided a compound of Formula (I)

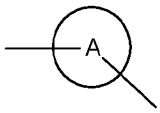


(I)

salts, racemates, diastereomers, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof

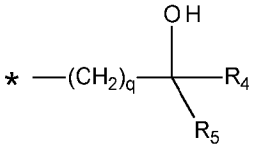
wherein

X_1 is N or C-R_1, preferably C-R_1 where R_1 is selected from H, OH, optionally substituted C_{1-3}alkyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{1-3}alkoxyl, halo, haloC_{1-3}alkyl, NH_2, optionally substituted NHC_{1-3}alkyl, optionally substituted $N(C_{1-3}alkyl)_2$, optionally substituted SC_{1-3}alkyl and CN;



represents Ring A which is selected from saturated or unsaturated monocyclic C_{3-7}cycloalkyl, saturated or unsaturated monocyclic 3-7 membered heterocycle, saturated or unsaturated fused bicyclic C_{8-10}cycloalkyl, saturated or unsaturated fused bicyclic 8-10 membered-heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl and may be optionally substituted;

Z_1 is a secondary or tertiary alcohol of general formula

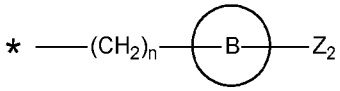


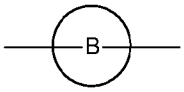
an ester, carbamate, phosphate, sulfate or prodrug thereof as defined below or Z_1 is selected from H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-6}$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl halo, optionally substituted haloC_{1-3}alkyl, CN and optionally substituted $(CH_2)_mNR^aR^b$ where each R^a and R^b is independently selected from H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted 4-6-membered heterocyclyl or R^a and R^b join together to form an optionally substituted 4-6-membered heterocyclyl and where each m is an integer independently selected from 0, 1, 2 and 3;

X_2 is N or C-R_2, preferably C-R_2 where R_2 is selected from H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-6}$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl, optionally substituted $(CH_2)_mO(CH_2)_mC_{3-7}$cycloalkyl, optionally substituted $(CH_2)_mC_{3-7}$cycloalkyl, optionally substituted $(CH_2)_mO(CH_2)_m$phenyl, optionally substituted $(CH_2)_m$phenyl, optionally substituted $(CH_2)_mO(CH_2)_m$-5-10-membered heterocycle, optionally substituted $(CH_2)_m$-5-10-membered heterocyclyl, halo, optionally substituted haloC_{1-3}alkyl, CN and optionally substituted $(CH_2)_mNR^aR^b$;

X_3 is N or C-R_3, preferably C-R_3 where R_3 is selected from H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-}$

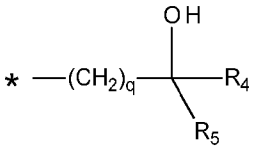
$_6$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl, optionally substituted $(CH_2)_mO(CH_2)_mC_{3-7}$cycloalkyl, optionally substituted $(CH_2)_mC_{3-7}$cycloalkyl, optionally substituted $(CH_2)_mO(CH_2)_m$phenyl, optionally substituted $(CH_2)_m$phenyl, optionally substituted $(CH_2)_mO(CH_2)_m$-5-10-membered heterocycle, optionally substituted $(CH_2)_m$-5-10-membered heterocyclyl, halo, optionally substituted haloC_{1-3}alkyl, CN and optionally substituted $(CH_2)_mNR^aR^b$ or R_3 is a group of formula

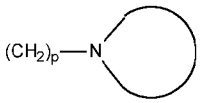


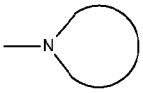
where * represents the point of attachment to the C ring atom; n is an integer selected from 0, 1, 2 and 3; 

represents Ring B which is selected from saturated or unsaturated monocyclic C_{3-7}cycloalkyl, saturated or unsaturated monocyclic 3-7 membered heterocycle, saturated or unsaturated fused bicyclic C_{8-10}cycloalkyl, saturated or unsaturated fused bicyclic 8-10 membered-heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl and may be optionally substituted; and

Z_2 is a secondary or tertiary alcohol of general formula

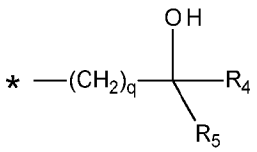


an ester, carbamate, phosphate, sulfate or prodrug thereof as defined below or Z_2 is selected from H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-6}$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl, CN, optionally substituted $(CH_2)_mNR^aR^b$, optionally substituted $(CH_2)_p$-4-6-membered heterocyclylic ring, optionally substituted $(CH_2)_p$-spiro-bicyclic-7-11-membered heterocyclic ring and optionally substituted 

where p is an integer selected from 0, 1, 2 and 3 and 

represents an optionally substituted 4-6 membered heterocyclic ring or an optionally substituted spiro bicyclic 7-11-membered heterocyclic ring; and

Alk is optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl; and with the proviso that Z_1 or Z_2 is a secondary or tertiary alcohol of general formula



an ester, carbamate, phosphate, sulfate or prodrug thereof

wherein q is an integer selected from 0, 1, 2 and 3, preferably q is 0;

R_4 is H or is selected from optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_tOC_{1-6}$alkyl, optionally substituted $(CH_2)_tOC(=O)C_{1-6}$alkyl, optionally substituted $(CH_2)_tSC_{1-6}$alkyl, optionally substituted $(CH_2)_tS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl and optionally substituted $(CH_2)_tNR^aR^b$;

R_5 is selected from optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-7}cycloalkyl ring, optionally substituted phenyl, optionally substituted 4-6-membered heterocyclyl ring, optionally substituted 5-6-membered heteroaryl ring, optionally substituted $(CH_2)_tOC_{1-6}$alkyl, optionally substituted $(CH_2)_tOC(=O)C_{1-6}$alkyl, optionally substituted $(CH_2)_tSC_{1-6}$alkyl, optionally substituted $(CH_2)_tS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl and optionally substituted $(CH_2)_tNR^aR^b$;

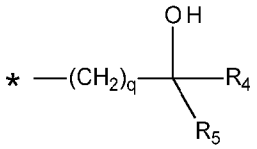
t is an integer selected from 1, 2, 3, 4, 5 and 6;

or R_4 and R_5 together with the carbon atom to which they are attached form an optionally substituted 4-6-membered heterocyclic ring or C_{3-7}cycloalkyl ring; and

* represents the point of attachment to Ring A or Ring B respectively; and further wherein each (CH_2) entity when present may be independently optionally substituted.

In one embodiment there is provided a compound of Formula (I), salts and prodrugs thereof.

In one embodiment Z_1 is a secondary or tertiary alcohol of general formula



or prodrug thereof wherein the prodrug is selected from an ester, carbamate, phosphate or sulfate formed from the hydroxyl moiety.

According to a second aspect there is provided a method for the treatment of a bacterial infection comprising administration of a compound of Formula (I) or a

pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulphate, deuterated form or prodrug thereof to a subject suffering from said infection. In one embodiment, the infection is a Gram positive bacterial infection. In a further embodiment the Gram positive infection is caused by a bacterial strain selected from *S. aureus, E. faecalis* and *S. pyogenes*, even more preferably *S. aureus*. In another embodiment, the infection is a Gram negative bacterial infection. In a further embodiment the Gram negative infection is caused by a bacterial strain of *H. influenzae, A. baumannii, E. coli, K. pneumoniae, Legionella pneumophila, Moraxella catarrhalis* and *Neisseria gonorrhoeae*.

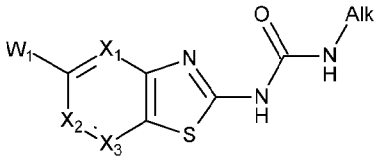
According to a third aspect there is provided a compound of Formula (I) or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulphate, deuterated form or prodrug thereof for use in the treatment of a bacterial infection.

According to a fourth aspect there is provided an antibacterial agent comprising a compound of Formula (I) or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulphate, deuterated form or prodrug thereof.

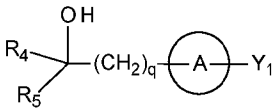
According to a fifth aspect there is provided a composition comprising a compound of Formula (I) or a salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulphate, deuterated form or prodrug thereof and an excipient or carrier. In one embodiment the composition is a pharmaceutical composition, the salt is a pharmaceutically acceptable salt and the excipient or carrier is pharmaceutically acceptable.

According to a sixth aspect there is provided a compound of Formula (I) or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulphate, deuterated form or prodrug thereof for use as a gyrase inhibitor. In one embodiment the compound of Formula (I) is active against the ATPase enzyme.

According to a seventh aspect there is provided a process for the manufacture of a compound of Formula (I), salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulphate, deuterated form or prodrug thereof comprising the step(s) of: coupling an intermediate of formula (i-a) with a precursor of formula (ii-a):



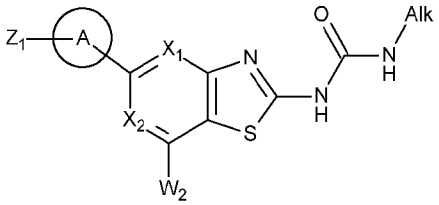
+



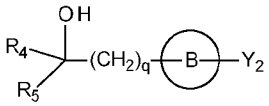
;

(i-a) (ii-a)

or alternatively coupling an intermediate of formula (i-b) with a precursor of formula (ii-b):



+



;

(i-b) (ii-b)

under coupling conditions wherein

W_1 and W_2 are selected from halo (preferably Cl, Br and I), boronic acid or a boronate ester thereof, a stannylated moiety and triflate;

Y_1 and Y_2 are selected from H, halo (preferably Cl, Br and I), boronic acid or a boronate ester thereof, a stannylated moiety and triflate; and

ring A, ring B, Alk, X_1, X_2, X_3, R_4, R_5 and q are as previously defined.

In one embodiment, the process comprises the additional step of forming an ester, carbamate, phosphate or sulphate of the hydroxyl (alcohol) moiety.

According to an eighth aspect, there is provided a method of treating bacterial contamination of a substrate comprising applying to the site of such contamination an amount of a compound of Formula (I) or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulphate, or deuterated form thereof sufficient to inhibit bacterial growth.

According to a ninth aspect, there is provided the use of a compound of Formula (I) or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulphate, deuterated form or prodrug thereof in the preparation of a medicament for the treatment of a bacterial infection in a subject.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1: Shows the intravenous (IV) pharmacokinetic profile in the rat assay, where the X axis denotes the time (hours) and the Y axis denotes the plasma concentration (μg/mL), of (A) comparative Compound A against Compounds **1** and

17 of the invention; and (B) comparative Compound B against Compound **27** of the invention.

FIGURE 2: Shows the comparative survival of mice dosed IV at 10 mg/kg with Compound 1 or Linezolid in the *S. pneumoniae* 9 day lung infection model where the X axis denotes the number of days and the Y axis denotes the percentage survival.

DETAILED DESCRIPTION

The present invention is predicated on the discovery of a new class of compounds that have shown on-target gyrase enzyme activity. Accordingly, in one embodiment the compounds of Formula (I) are useful in modulating the activity of gyrase, more particularly as gyrase inhibitors.

Compounds of this class also exhibit antibacterial activity, more particularly antibacterial activity against strains of Gram-positive and/or Gram-negative classes, such as staphylococci, enterococci, streptococci and haemophili for example *Staphylococcus aureus*, *Staphylococcus epidermidis, Enterococcus faecalis, Enterococcus faecium, Streptococcus pyogenes, Streptococcus pneumoniae, Haemophilus influenzae, Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis* and *Neisseria gonorrhoeae*. The compounds with which the invention is concerned are therefore useful for the treatment of bacterial infection or contamination, for example in the treatment of, *inter alia*, Gram-positive infections, Gram-negative infections and community acquired bacterial pneumonias (CABPs), hospital acquired bacterial pneumonias (HABPs) and ventilator acquired bacterial pneuomias (VABPs). Accordingly, in one embodiment the compounds of Formula (I) are useful in the treatment of bacterial infections caused by Gram positive bacterial strains. In another embodiment, the compounds of Formula (I) are useful in the treatment of bacterial infections caused by Gram negative bacterial strains. The sites of bacterial infections are many and include respiratory infections, particularly lung infections, skin and skin structure infections, urinary tract infections, intra-abdominal infections and blood stream (septicaemia) infections.

The development of antibacterial resistance is particularly common in a hospital setting. Hospital patients are therefore especially at risk of infection by resistant strains of bacteria.

Definitions

Unless otherwise herein defined, the following terms will be understood to have the general meanings which follow.

The term "C_{1-6}alkyl" encompasses optionally substituted straight chain or branched chain hydrocarbon groups having from 1, 2, 3, 4, 5 or 6 carbon atoms or a range comprising any of two of those integers. Examples include methyl (Me), ethyl (Et), propyl (Pr), isopropyl (*i*-Pr), butyl (Bu), isobutyl (*i*-Bu), sec-butyl (*s*-Bu), tert-butyl (*t*-Bu), pentyl, neopentyl, hexyl and the like. Unless the context requires otherwise, the term "C_{1-6}alkyl" also encompasses alkyl groups containing one less hydrogen atom such that the group is attached via two positions i.e. divalent. Such groups are also referred to as "C_{1-6}alkylene" groups. C_{1-3}alkyl and C_{1-3}alkylene groups are preferred.

The term "C_{2-6}alkenyl" refers to optionally substituted straight chain or branched chain hydrocarbon groups having at least one double bond of either *E* or *Z* stereochemistry where applicable and 2, 3, 4, 5 or 6 carbon atoms or a range comprising any of two of those integers. Examples include vinyl, 1-propenyl, 1- and 2-butenyl, 2-methyl-2-propenyl, hexenyl, butadienyl, hexadienyl, hexatrienyl and the like. Unless the context requires otherwise, the term "C_{1-6}alkenyl" also encompasses alkenyl groups containing one less hydrogen atom such that the group is attached via two positions i.e. divalent. Such groups are also referred to as "C_{2-6}alkenylene" groups. C_{2-3}alkenyl and C_{2-3}alkenylene groups are preferred.

The term "C_{2-6}alkynyl" refers to optionally substituted straight chain or branched chain hydrocarbon groups having at least one triple bond and 2, 3, 4, 5 or 6 carbon atoms or a range comprising any of two of those integers. Examples include ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. Unless the context indicates otherwise, the term "C_{2-6}alkynyl" also encompasses alkynyl groups containing one less hydrogen atom such that the group is attached via two positions i.e. divalent. Such groups are also referred to as "C_{2-6}alkynylene" groups. C_{2-3}alkynyl and C_{2-3}alkynylene groups are preferred.

The term "C_{3-8}cycloalkyl" refers to non-aromatic cyclic hydrocarbon groups having from 3, 4, 5, 6, 7 or 8 carbon atoms or a range comprising any of two of those integers, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl and the like. It will be understood that cycloalkyl groups may be saturated such as cyclohexyl or unsaturated such as cyclohexenyl. C_{3-6}cycloalkyl groups are preferred.

The terms “hydroxy” and “hydroxyl” refer to the group -OH.

The term “oxo” refers to the group =O.

The term “C_{1-6}alkoxyl” refers to the group OC_{1-6}alkyl. Examples include methoxy, ethoxy, propoxy, isoproxy, butoxy, tert-butoxy, pentoxy and the like. The oxygen atom may be located along the hydrocarbon chain, and need not be the atom linking the group to the remainder of the compound. C_{1-3}alkoxyl groups are preferred.

The term “aryloxy” refers to the group –Oaryl and may include variations thereof such as “alkoxyaryl”, wherein aryl is defined herein. Examples include, but are not limited to, phenoxy and naphthoxy and benzyloxy.

The terms “halo”, “halogen”, “halogenated” and similar terms refers to fluoro, chloro, bromo and iodo (F, Cl, Br, I).

The term “C_{1-6}alkylhalo” refers to a C_{1-6}alkyl which is substituted with one or more halogens. C_{1-3}alkylhalo groups are preferred, such as for example, $-CHF_2$ and $-CF_3$.

The term “C_{1-6}alkoxylhalo” refers to a C_{1-6}alkoxyl which is substituted with one or more halogens. C_{1-3}alkoxylhalo groups are preferred, such as for example, $-OCHF_2$ and $-OCF_3$.

The term “carboxylate” or “carboxyl” refers to the group $-COO^-$ or -COOH.

The term “ester” refers to a carboxyl group having the hydrogen replaced with, for example a C_{1-6}alkyl group (“carboxylC_{1-6}alkyl” or “alkylester”), an aryl or aralkyl group (“arylester” or “aralkylester”) and so on. Examples include but are not limited to CO_2C_{1-3}alkyl, such as for example, methylester (CO_2Me), ethylester (CO_2Et) and propylester (CO_2Pr) and includes reverse esters thereof (e.g. –OCOMe, -OCOEt and –OCOPr).

The term “cyano” refers to the group -CN.

The term “nitro” refers to the group $-NO_2$.

The term “amino” refers to the group $-NH_2$.

The term “substituted amino” or “secondary amino” refers to an amino group having a hydrogen replaced with, for example a C_{1-6}alkyl group (“C_{1-6}alkylamino”), an aryl or aralkyl group (“arylamino”, “aralkylamino”) and so on. C_{1-3}alkylamino groups are preferred, such as for example, methylamino (NHMe), ethylamino (NHEt) and propylamino (NHPr).

The term “disubstituted amino” or “tertiary amino” refers to an amino group having the two hydrogens replaced with, for example a C_{1-6}alkyl group, which may be the same or different (“dialkylamino”), an aryl and alkyl group (“aryl(alkyl)amino”) and

so on. Di(C_{1-3}alkyl)amino groups are preferred, such as for example, dimethylamino (NMe_2), diethylamino (NEt_2), dipropylamino (NPr_2) and variations thereof (e.g. N(Me)(Et) and so on).

The term "acyl" or "aldehyde" refers to the group -C(=O)H.

The term "substituted acyl" or "ketone" refers to an acyl group having a hydrogen replaced with, for example a C_{1-6}alkyl group ("C_{1-6}alkylacyl" or "alkylketone" or "ketoalkyl"), an aryl group ("arylketone"), an aralkyl group ("aralkylketone") and so on. C_{1-3}alkylacyl groups are preferred.

The term "amido" or "amide" refers to the group -C(O)NH_2.

The term "aminoacyl" refers to the group -NHC(O)H.

The term "substituted amido" or "substituted amide" refers to an amido group having a hydrogen replaced with, for example a C_{1-6}alkyl group ("C_{1-6}alkylamido" or "C_{1-6}alkylamide"), an aryl ("arylamido"), aralkyl group ("aralkylamido") and so on. C_{1-3}alkylamide groups are preferred, such as for example, methylamide (-C(O)NHMe), ethylamide (-C(O)NHEt) and propylamide (-C(O)NHPr) and includes reverse amides thereof (e.g. -NHMeC(O)-, -NHEtC(O)- and -NHPrC(O)-).

The term "disubstituted amido" or "disubstituted amide" refers to an amido group having the two hydrogens replaced with, for example a C_{1-6}alkyl group ("di(C_{1-6}alkyl)amido") or "di(C_{1-6}alkyl)amide"), an aralkyl and alkyl group ("alkyl(aralkyl)amido") and so on. Di(C_{1-3}alkyl)amide groups are preferred, such as for example, dimethylamide (-C(O)NMe_2), diethylamide (-C(O)NEt_2) and dipropylamide (-C(O)NPr_2) and variations thereof (e.g. -C(O)N(Me)Et and so on) and includes reverse amides thereof.

The term "carbamic acid" refers to the group NH_2CO_2H.

The term "carbamate" refers to a carbamic acid group having one or both amino hydrogens independently replaced with, for example a C_{1-6}alkyl group ("C_{1-6}alkyl carbamate"), an aryl ("arylcarbamate"), aralkyl group ("aralkylcarbamate") and so on.

The term "thiol" refers to the group -SH.

The term "C_{1-6}alkylthio" refers to a thiol group having the hydrogen replaced with a C_{1-6}alkyl group. C_{1-3}alkylthio groups are preferred, such as for example, thiolmethyl, thiolethyl and thiolpropyl.

The term "thioxo" refers to the group =S.

The term "sulfinyl" refers to the group -S(=O)H.

The term "substituted sulfinyl" or "sulfoxide" refers to a sulfinyl group having the hydrogen replaced with, for example a C_{1-6}alkyl group ("C_{1-6}alkylsulfinyl" or "C_{1-6}alkylsulfoxide"), an aryl ("arylsulfinyl"), an aralkyl ("aralkyl sulfinyl") and so on. C_{1-3}alkylsulfinyl groups are preferred, such as for example, -SOmethyl, -SOethyl and -SOpropyl.

The term "sulfonyl" refers to the group $-SO_2H$.

The term "substituted sulfonyl" refers to a sulfonyl group having the hydrogen replaced with, for example a C_{1-6}alkyl group ("sulfonylC_{1-6}alkyl"), an aryl ("arylsulfonyl"), an aralkyl ("aralkylsulfonyl") and so on. SulfonylC_{1-3}alkyl groups are preferred, such as for example, $-SO_2Me$, $-SO_2Et$ and $-SO_2Pr$.

The term "sulfonylamido" or "sulfonamide" refers to the group $-SO_2NH_2$.

The term "substituted sulfonamido" or "substituted sulphonamide" refers to an sulfonylamido group having a hydrogen replaced with, for example a C_{1-6}alkyl group ("sulfonylamidoC_{1-6}alkyl"), an aryl ("arylsulfonamide"), aralkyl ("aralkylsulfonamide") and so on. SulfonylamidoC_{1-3}alkyl groups are preferred, such as for example, $-SO_2NHMe$, $-SO_2NHEt$ and $-SO_2NHPr$ and includes reverse sulfonamides thereof (e.g. $-NHSO_2Me$, $-NHSO_2Et$ and $-NHSO_2Pr$).

The term "disubstituted sulfonamido" or "disubstituted sulphonamide" refers to a sulfonylamido group having the two hydrogens replaced with, for example a C_{1-6}alkyl group, which may be the same or different ("sulfonylamidodi(C_{1-6}alkyl)"), an aralkyl and alkyl group ("sulfonamido(aralkyl)alkyl") and so on. Sulfonylamidodi(C_{1-3}alkyl) groups are preferred, such as for example, $-SO_2NMe_2$, $-SO_2NEt_2$ and $-SO_2NPr_2$ and variations thereof (e.g. $-SO_2N(Me)Et$ and so on) and includes reverse sulfonamides thereof.

The term "sulfate" refers to the group $OS(O)_2OH$ and includes groups having the hydrogen replaced with, for example a C_{1-6}alkyl group ("alkylsulfates"), an aryl ("arylsulfate"), an aralkyl ("aralkylsulfate") and so on. C_{1-3}sulfates are preferred, such as for example, $OS(O)_2OMe$, $OS(O)_2OEt$ and $OS(O)_2OPr$.

The term "sulfonate" refers to the group SO_3H and includes groups having the hydrogen replaced with, for example a C_{1-6}alkyl group ("alkylsulfonate"), an aryl ("arylsulfonate"), an aralkyl ("aralkylsulfonate") and so on. C_{1-3}sulfonates are preferred, such as for example, SO_3Me, SO_3Et and SO_3Pr.

The term "phosphate" refers to a group $-OP(O)(OH)_2$ and includes groups having each hydrogen independently replaced with, for example a C_{1-6}alkyl group

("alkylphosphate"), an aryl ("arylphosphate"), an aralkyl ("aralkylphosphate") and so on.

The term "phosphonate" refers to a group $-P(O)(OH)_2$ and includes groups having each hydrogen independently replaced with, for example a C_{1-6}alkyl group ("alkylphosphonate"), an aryl ("arylphosphonate"), an aralkyl ("aralkylphosphpmate") and so on.

The term "aryl" refers to any group containing a carbocyclic (non-heterocyclic) aromatic ring and may be a mono-, bi- or tri-cyclic ring system. The aromatic ring or ring system is generally composed of 6 or 10 carbon atoms. Such groups may contain fused ring systems (such as naphthyl, tetrahydronaphthyl, fluorenyl, indenyl, azulenyl, anthracenyl and the like), linked ring systems (such as biphenyl groups), and may be substituted or unsubstituted. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and tetrahydronaphthyl. Phenyl is preferred.

The term "aralkyl" refers to an aryl group substituted with a C_{1-6}alkyl group. Examples include benzyl and phenethyl.

The term "heterocyclyl" refers to a moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound which moiety has from 3 to 10 ring atoms (unless otherwise specified), of which 1, 2, 3 or 4 are ring heteroatoms each heteroatom being independently selected from O, S and N.

In this context, the prefixes 3-, 4-, 5-, 6-, 7-, 8-, 9- and 10- membered denote the number of ring atoms, or range of ring atoms, whether carbon atoms or heteroatoms. For example, the term "3-10 membered heterocyclyl", as used herein, pertains to a heterocyclyl group having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms or a range comprising any of two of those integers. Examples of heterocyclyl groups include 5-6-membered monocyclic heterocyclyls and 9-10 membered fused bicyclic heterocyclyls.

Examples of monocyclic heterocyclyl groups include, but are not limited to, those containing one nitrogen atom such as aziridine (3-membered ring), azetidine (4-membered ring), pyrrolidine (tetrahydropyrrole), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) or pyrrolidinone (5-membered rings) , piperidine, dihydropyridine, tetrahydropyridine (6-membered rings), and azepine (7-membered ring); those containing two nitrogen atoms such as imidazoline, pyrazolidine (diazolidine), imidazoline, pyrazoline (dihydropyrazole) (5-membered rings), piperazine (6-membered ring); those containing one oxygen atom such as oxirane (3-membered ring), oxetane (4-membered ring), oxolane

(tetrahydrofuran), oxole (dihydrofuran) (5-membered rings), oxane (tetrahydropyran), dihydropyran, pyran (6-membered rings), oxepin (7-membered ring); those containing two oxygen atoms such as dioxolane (5-membered ring), dioxane (6-membered ring), and dioxepane (7-membered ring); those containing three oxygen atoms such as trioxane (6-membered ring); those containing one sulfur atom such as thiirane (3-membered ring), thietane (4-membered ring), thiolane (tetrahydrothiophene) (5-membered ring), thiane (tetrahydrothiopyran) (6-membered ring), thiepane (7-membered ring); those containing one nitrogen and one oxygen atom such as tetrahydrooxazole, dihydrooxazole, tetrahydroisoxazole, dihydroisoxazole (5-membered rings), morpholine, tetrahydrooxazine, dihydrooxazine, oxazine (6-membered rings); those containing one nitrogen and one sulfur atom such as thiazoline, thiazolidine (5-membered rings), thiomorpholine (6-membered ring); those containing two nitrogen and one oxygen atom such as oxadiazine (6-membered ring); those containing one oxygen and one sulfur such as: oxathiole (5-membered ring) and oxathiane (thioxane) (6-membered ring); and those containing one nitrogen, one oxygen and one sulfur atom such as oxathiazine (6-membered ring).

Heterocyclyls also encompass aromatic heterocyclyls and non-aromatic heterocyclyls. Such groups may be substituted or unsubstituted.

The term “aromatic heterocyclyl” may be used interchangeably with the term “heteroaromatic” or the term “heteroaryl” or “hetaryl”. The heteroatoms in the aromatic heterocyclyl group may be independently selected from N, S and O. “Heteroaryl” is used herein to denote a heterocyclic group having aromatic character and embraces aromatic monocyclic ring systems and polycyclic (e.g. bicyclic) ring systems containing one or more aromatic rings. The term aromatic heterocyclyl also encompasses pseudoaromatic heterocyclyls. The term “pseudoaromatic” refers to a ring system which is not strictly aromatic, but which is stabilized by means of delocalization of electrons and behaves in a similar manner to aromatic rings. The term aromatic heterocyclyl therefore covers polycyclic ring systems in which all of the fused rings are aromatic as well as ring systems where one or more rings are non-aromatic, provided that at least one ring is aromatic. In polycyclic systems containing both aromatic and non-aromatic rings fused together, the group may be attached to another moiety by the aromatic ring or by a non-aromatic ring.

Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to ten ring members. The heteroaryl group can be, for example, a five membered

or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or two fused five membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulfur and oxygen. The heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Aromatic heterocyclyl groups may be 5-membered or 6-membered mono-cyclic aromatic ring systems.

Examples of 5-membered monocyclic heteroaryl groups include but are not limited to furanyl, thienyl, pyrrolyl, oxazolyl, oxadiazolyl (including 1,2,3 and 1,2,4 oxadiazolyls and furazanyl i.e. 1,2,5-oxadiazolyl), thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl (including 1,2,3, 1,2,4 and 1,3,4 triazolyls), oxatriazolyl, tetrazolyl, thiadiazolyl (including 1,2,3 and 1,3,4 thiadiazolyls) and the like.

Examples of 6-membered monocyclic heteroaryl groups include but are not limited to pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, oxazinyl, dioxinyl, thiazinyl, thiadiazinyl and the like. Examples of 6-membered heteroaryl groups containing nitrogen include pyridyl (1 nitrogen), pyrazinyl, pyrimidinyl and pyridazinyl (2 nitrogens). It will be understood that, such as in the case of pyridyl when substituted with an oxo (=O) substituted the group may be interchangeably referred to as a pyridinone group.

Aromatic heterocyclyl groups may also be bicyclic or polycyclic heteroaromatic ring systems such as fused ring systems (including purine, pteridinyl, napthyridinyl, 1H thieno[2,3-c]pyrazolyl, thieno[2,3-b]furyl and the like) or linked ring systems (such as oligothiophene, polypyrrole and the like). Fused ring systems may also include aromatic 5-membered or 6-membered heterocyclyls fused to carbocyclic aromatic rings such as phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl and the like, such as 5- or 6- membered aromatic heterocyclyls fused to a phenyl ring including 5-membered aromatic heterocyclyls containing nitrogen fused to a phenyl ring, 5-membered aromatic heterocyclyls containing 1 or 2 nitrogens fused to a phenyl ring

and such as 5- or 6- membered aromatic heteroaryls fused to a 6- membered aromatic or non-aromatic heterocyclyls.

A bicyclic heteroaryl group may be, for example, a group selected from: a) a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; b) a pyridine ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; c) a pyrimidine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; d) a pyrrole ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; e) a pyrazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; f) an imidazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; g) an oxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; h) an isoxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; i) a thiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; j) an isothiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; k) a thiophene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; l) a furan ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; m) a cyclohexyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; and n) a cyclopentyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms.

Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring i.e. 8-membered fused bicyclic rings include but are not limited to imidazothiazole (e.g. imidazo[2,1-b]thiazole) and imidazoimidazole (e.g. imidazo[1,2-a]imidazole).

Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring i.e. 9-membered fused bicyclic rings include but are not limited to benzofuran, benzothiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzothiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, imidazopyridine (e.g. imidazo[1,2-a]pyridine and imidazo[4,5-b]pyridine], pyrazolopyrimidine (e.g. pyrazolo[1,5-a]pyrimidine), benzodioxole and pyrazolopyridine (e.g. pyrazolo[1,5-a]pyridine) groups. A further example of a six membered ring fused to a five membered ring is a pyrrolopyridine group such as a pyrrolo[2,3-b]pyridine group.

Particular examples of bicyclic heteroaryl groups containing two fused six membered rings i.e. 10-membered fused bicyclic rings include but are not limited to quinoline,

isoquinoline, chroman, thiochroman, chromene (including optionally substituted with oxo (=O) i.e. oxochromene), isochromene, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups.

Examples of heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthalene, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzothiophene, dihydrobenzofuran, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, indoline, isoindoline and indane groups.

Examples of aromatic heterocyclyls fused to carbocyclic aromatic rings may therefore include but are not limited to benzothiophenyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzimidazolyl, indazolyl, benzoxazolyl, benzisoxazolyl, isobenzoxazoyl, benzothiazolyl, benzisothiazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzotriazinyl, phthalazinyl, carbolinyl and the like.

The term “non-aromatic heterocyclyl” encompasses optionally substituted saturated and unsaturated rings which contain at least one heteroatom selected from the group consisting of N, S and O.

Non-aromatic heterocyclyls may be 3-7 membered mono-cyclic rings.The term “3-7 membered monocyclic”, as used herein, pertains to a mono-cyclic group having 3, 4, 5, 6 or 7 ring atoms or a range comprising any of two of those integers. Examples of 5-membered non-aromatic heterocyclyl rings include 2H-pyrrolyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolinyl, 2-pyrazolinyl, 3-pyrazolinyl, pyrazolidinyl, 2-pyrazolidinyl, 3-pyrazolidinyl, imidazolidinyl, 3-dioxalanyl, thiazolidinyl, isoxazolidinyl, 2-imidazolinyl and the like.

Examples of 6-membered non-aromatic heterocyclyls include piperidinyl, piperidinonyl, pyranyl, dihyrdopyranyl, tetrahydropyranyl, 2H pyranyl, 4H pyranyl, thianyl, thianyl oxide, thianyl dioxide, piperazinyl, diozanyl, 1,4-dioxinyl, 1,4-dithianyl, 1,3,5-triozalanyl, 1,3,5-trithianyl, 1,4-morpholinyl, thiomorpholinyl, 1,4-oxathianyl, triazinyl, 1,4-thiazinyl and the like.

Examples of 7-membered non-aromatic heterocyclyls include azepanyl, oxepanyl, thiepanyl and the like.

Non-aromatic heterocyclyl rings may also be bicyclic heterocyclyl rings such as linked ring systems (for example uridinyl and the like) or fused ring systems. Fused ring systems include non-aromatic 5-membered, 6-membered or 7-membered heterocyclyls fused to carbocyclic aromatic rings such as phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl and the like. Examples of non-aromatic 5-membered, 6-membered or 7-membered heterocyclyls fused to carbocyclic aromatic rings include indolinyl, benzodiazepinyl, benzazepinyl, dihydrobenzofuranyl and the like.

The term "spiro ring system" means a bicyclic ring system in which the rings are connected via a single shared atom or "spiroatom" more particularly a quaternery carbon ("spiro carbon") and encompasses spiro bicyclic 7-11- membered carbocyclic rings and spiro bicyclic 7-11- membered heterocyclic rings containing one, two, three or four heteroatoms independently selected from O, N and S.

The term "derived from an amino acid" refers to any side chain that may be present in natural (L-) or unnatural (D-) amino acids. Examples of amino acid side chain moieties derived from natural amino acids, with the amino acids from which they are derived shown in brackets, are -H (Glycine), $-CH_3$ (Alanine), $-CH(CH_3)_2$ (Valine), $-CH_2CH(CH_3)_2$ (Leucine), $-CH(CH_3)CH_2CH_3$ (Isoleucine), $-(CH_2)_4NH_2$ (Lysine), $-(CH_2)_3NHC(=NH)NH_2$ (Arginine), $-CH_2$-(5-1 H-imidazolyl) (Histidine), $-CH_2CONH_2$ (Asparagine), $-CH_2CH_2CONH_2$ (Glutamine), $-CH_2COOH$ (Aspartic acid), $-CH_2CH_2COOH$ (Glutamic acid), $-CH_2$-phenyl (Phenylalanine), $-CH_2$-(4-OH-phenyl) (Tyrosine), $-CH_2$-(3-1 H-indolyl) (Tryptophan), $-CH_2SH$ (Cysteine), $-CH_2CH_2SCH_3$ (Methioine), $-CH_2OH$ (Serine), $-CH(OH)CH_3$ (Threonine) and the cyclic side chain pyrrolidinyl (Proline) whereby the covalent bond between the nitrogen and carbon in the pyrrolidinyl ring forms the backbone. Examples of amino acid side chain moieties derived from unnatural amino acids, with the amino acids from which they are derived shown in brackets, are $-(CH_2)_2-C(O)-O-C(CH_3)_3$ (glutamic acid t- butyl ester), $-(CH_2)_4-NH-C(O)-O-C(CH_3)_3$ (N_ε-(tert-butoxycarbonyl)-lysine), $-(CH_2)_3-NH-C(O)NH_2$ (citrulline), $-CH_2-CH_2OH$ (homoserine) and $-(CH_2)_2-CH_2NH_2$ (ornithine). Examples can also include alkyl, alkenyl, alkynyl, aryl, saturated and unsaturated heterocycles (functionalized and unfunctionalized). The term "amino-acid side chain moiety" can also include a number of unnatural amide and sulfonamide, aryl and heteroaryl side chains.

Unless otherwise defined, the term "optionally substituted" or "optional substituent" as used herein refers to a group which may or may not be further substituted with 1, 2,

3, 4 or more groups, preferably 1, 2 or 3, more preferably 1 or 2 groups selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, hydroxyl, oxo, C_{1-6}alkoxy, aryloxy, C_{1-6}alkoxyaryl, halo, C_{1-6}alkylhalo (such as CF_3 and CHF_2), C_{1-6}alkoxyhalo (such as OCF_3 and $OCHF_2$), carboxylic acid, carboxyl, esters, cyano, nitro, amino, mono substituted amino, disubstituted amino, acyl, ketones, amides, aminoacyl, substituted amides, disubstituted amides, carbamic acid, carbamates, thiol, alkylthio, thioxo, sulfates, sulfonates, sulfinyl, substituted sulfinyl, sulfonyl, substituted sulfonyl, sulfonylamides, substituted sulfonamides, disubstituted sulfonamides, phosphates, phosphonates, aryl, arC_{1-6}alkyl, heterocyclyl, heteroaryl and spiro ring systems wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl and spiro ring system and groups containing them may be further optionally substituted. Unless otherwise defined, particularly preferred optional substituents in one embodiment of the invention include 1, 2, 3 or 4, preferably 1 or 2 substituents each independently selected from the group consisting of C_{1-4}alkyl (particularly methyl), halo (particularly F), haloC_{1-3}alkyl (particularly CHF_2 and CF_3), OH, C_{1-4}alkoxyl (particularly OCH_3), CO_2H, CO_2C_{1-4}alkyl (particularly CO_2CH_3), NH_2, NHC_{1-4}alkyl (particularly $NHCH_3$), $N(C_{1-4}alkyl)_2$ (particularly $N(CH_3)_2$), NHC(=O)C_{1-4}alkyl, NHC(=O)-4-6-membered heterocyclyl, OP(=O)$(OR)_2$ (where each R is independently H or C_{1-4}alkyl), P(=O)$(OR)_2$ (where each R is independently H or C_{1-4}alkyl), C_{3-6}cycloalkyl (particularly cyclopropyl, cyclobutyl, cyclopenyl and cyclohexyl), phenyl, 4-6-membered heterocylyl (particularly oxetanyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, oxothiazinyl, dioxothiazinyl, thianyl (also known as tetrahydrothiopyranyl), oxothianyl, dioxothianyl, piperidinyl, and piperazinyl) and further where C_{1-4}alkyl either alone or as part of a substituent group includes methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl and may be further optionnally substituted.

Optional substituents in the case of heterocycles, heteroaryls and spiro bicyclic heterocyclic ring systems containing N may also include but are not limited to alkyl i.e. *N*-C_{1-3}alkyl, more preferably methyl, particularly *N*-methyl.

It will be understood that suitable derivatives of aromatic heterocyclyls containing nitrogen include *N*-oxides thereof.

Embodiments will now be described with reference to the following non-limiting examples.

Compounds

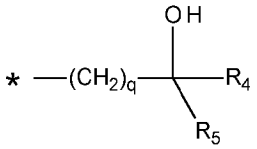
In one embodiment Alk is optionally substituted C_{1-6}alkyl, preferably C_{1-3}alkyl and even more preferably is unsubstituted ethyl.

In one embodiment X_1 is C-R_1, X_2 is C-R_2 and X_3 is C-R_3.

In one embodiment X_1 is C-R_1 and R_1 is H or halo, preferably H.

In one embodiment ring A is an optionally substituted 5-6-membered heteroaryl, preferably containing at least one N heteroatom. In one embodiment ring A is a 5-membered heteroaryl. Preferred 5-membered heteoaryl include triazolyl, imidazolyl and thiazolyl rings. In one embodiment, ring A is a 6-membered heteoaryl with pyrimidine, pyridine and pyrazine rings being most preferred.

In one embodiment Z_1 is a secondary or tertiary alcohol of general formula



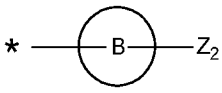
an ester, carbamate, phosphate, sulfate or prodrug thereof wherein q, R_4 and R_5 are as previously defined.

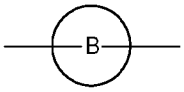
In one embodiment X_2 is C-R_2 where R_2 is H. In another embodiment X_2 is C-R_2 where R_2 is selected from H,OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted OC_{1-6}alkyl, optionally substituted SC_{1-6}alkyl, optionally substituted $S(=O)C_{1-6}$alkyl, an optionally substituted 5-6-membered heterocycle, halo, haloC_{1-3}alkyl, CN and optionally substituted $(CH_2)_mNR^aR^b$.

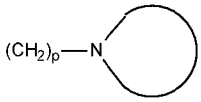
In one embodiment R_2 is selected from H, halo preferably F, OH, optionally substituted NHC_{1-3}alkyl (preferably $NHCH_3$ or $NHCH_2CH_3$), optionally substituted $N(C_{1-3}alkyl)_2$ (preferably $N(CH_3)_2$ or $N(CH_3)CH_2CH_3$), optionally substituted SC_{1-3}alkyl (preferably SCH_2CH_3), optionally substituted $S(=O)C_{1-3}$alkyl (preferably $S(=O)CH_2CH_3$), an optionally substituted 6-membered heterocycle (preferably 6-membered such as morpholine) and optionally substituted OC_{1-3}alkyl (preferably methoxy or ethoxy) wherein the optional substituents may be, for example OH, methoxy, C_{3-6}cycloalkyl (e.g. such as cyclopropyl), phenyl or a 5-6-membered heterocycle (e.g. such as tetrahydrofuran, tetrahydropyran, pyrrolidine, pyrazolidine, imidazolidine, piperidine, piperazine and morpholine).

In one embodiment X_3 is C-R_3 where R_3 is H.

In another embodiment X_3 is C-R_3 where R_3 is selected from optionally substituted C_{1-6}alkyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted

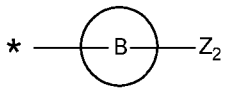
$(CH_2)_mNR^aR^b$ or is a group of formula 

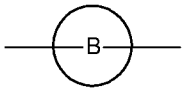
where * represents the point of attachment to the carbon ring atom; 

represents Ring B which is selected from saturated or unsaturated monocyclic 3-7 membered heterocycle, saturated or unsaturated fused bicyclic 8-10 membered-heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl and may be optionally substituted; and Z_2 is a secondary or tertiary alcohol or Z_2 is selected from H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mNR^aR^b$, optionally substituted $(CH_2)_p$-4-6-membered heterocyclylic ring, optionally substituted $(CH_2)_p$-spiro-bicyclic-7-11-membered heterocyclic ring and optionally substituted 

.

In a further embodiment R_3 is selected from optionally substituted C_{1-3}alkyl, optionally substituted OC_{1-3}alkyl, optionally substituted $(CH_2)_mNH_2$, optionally substituted $(CH_2)_mNHC_{1-3}$alkyl and optionally substituted $(CH_2)_mN(C_{1-3}alkyl)_2$. In still a further particular embodiment R_3 is selected from optionally substituted methyl (such as optionally substituted with methoxy, dimethylamino or a 6-membered heterocycylic group such as morpholinyl) or optionally substituted methoxy (such as optionally substituted with pyridyl wherein pyridyl is further optionally substituted with methyl).

In another embodiment R_3 is a group of formula 

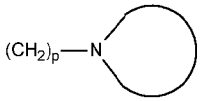
where * represents the point of attachment to the carbon ring atom; 

represents Ring B which is selected from saturated or unsaturated monocyclic 5-6 membered heterocycle (such as pyrrolidinyl and morpholinyl), C_6aryl and 5-6 membered heteroaryl and may be optionally substituted.

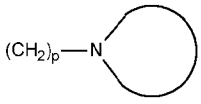
In a preferred embodiment Ring B is an optionally substituted 5-6 membered heteroaryl, with 6-membered heteroaryl being particularly preferred and 6-membered

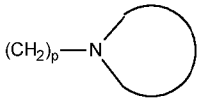
heteroaryl selected from pyridine, pyridazine, pyrimidine and pyrazine being most preferred.

In one embodiment Z_2 is H.

In one embodiment Z_2 is selected from OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-6}$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl, $(CH_2)_mNH_2$, optionally substituted $(CH_2)_mNHC_{1-6}$alkyl, optionally substituted $(CH_2)_mN(C_{1-6}alkyl)_2$, optionally substituted $(CH_2)_p$-4-6-membered heterocyclic ring, optionally substituted $(CH_2)_p$-spiro-bicyclic-7-11-membered heterocyclic ring and optionally substituted 

.

In a further embodiment Z_2 is selected from OH, halo (particulary F), an optionally substituted C_{1-6}alkyl (particularly methyl, ethyl and propyl, most preferably methyl), optionally substituted OC_{1-6}alkyl (particulary methoxy, ethoxy and propoxy), halo (particulary F), $(CH_2)_mNH_2$ (particulary NH_2), optionally substituted $(CH_2)_mNHC_{1-3}$alkyl (particularly $NHCH_3$ and $NHCH_2CH_3$), optionally substituted $(CH_2)_mNHC_{3-6}$cycloalkyl (particularly CH_2NHC_{3-6}cycloalkyl such as CH_2NHcyclopropyl and NHC_{3-6}cycloalkyl such as NH-cyclohexyl) optionally substituted $(CH_2)_mN(C_{1-3}alkyl)_2$ (particulary $N(CH_3)_2$ and $N(CH_3)CH_2CH_3$), optionally substituted $(CH_2)_p$-4-6-membered heterocyclic ring, optionally substituted $(CH_2)_p$-spiro-bicyclic-7-11-membered heterocyclic ring and optionally substituted 

. In still another embodiment Z_2 is optionally substituted 

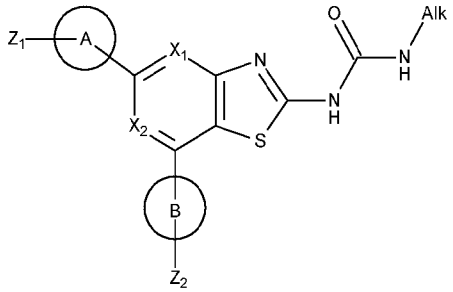
where p is 0, 1 or 2, preferably 0 or 1, even more preferably is 1.

In a particulary preferred embodiment Z_2 is an optionally substituted $(CH_2)_p$-4-6-membered heterocyclic ring or optionally substituted $(CH_2)_p$-spiro-bicyclic-7-11-membered heterocyclic ring where p is an integer selected from 0, 1 and 2, preferably 0 or 1. Particularly preferred 4-6-membered heterocyclic rings contain at least one nitrogen heteroatom and include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxothiazinyl and dioxothiazinyl and further may be

optionally substituted. Particulary preferred spiro-bicyclic-7-11-membered heterocyclic rings include oxa-azaspiroheptane and oxa-azaspirononane and may be optionally substituted.

Suitable optional substituents for Z_2 include but are not limited to one or more substituents, preferably 1 or 2 substituents independently selected from OH, C_{1-3}alkyl (particularly methyl), C_{1-3}alkoxyl (particulary methoxy), halo (particularly F), CO_2H, CO_2C_{1-3}alkyl (particularly CO_2CH_3), $P(=O)(OH)_2$ and $P(=O)(OC_{1-3}alkyl)_2$.

In one embodiment the compound is of Formula (Ia)

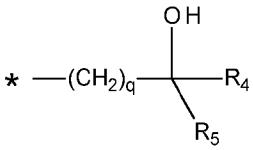


(Ia)

salts, isomers, racemates, diastereomers, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof

wherein X_1, X_2, Alk, Ring A, Ring B, Z_1 and Z_2 are as previously defined.

In one embodiment Z_1 is a secondary or tertiary alcohol of general formula



or an ester, carbamate, phosphate, sulfate or prodrug thereof

wherein q is an integer selected from 0, 1, 2 or 3 and each (CH_2) entity when present may be independently optionally substituted;

R_4 is H or is selected from optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_tOC_{1-6}$alkyl, optionally substituted $(CH_2)_tOC(=O)C_{1-6}$alkyl, optionally substituted $(CH_2)_tSC_{1-6}$alkyl, optionally substituted $(CH_2)_tS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl and optionally substituted $(CH_2)_tNR^aR^b$;

R_5 is selected from optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-7}cycloalkyl ring, optionally substituted phenyl, optionally substituted 4-6-membered heterocyclyl ring,

optionally substituted 5-6-membered heteroaryl ring, optionally substituted $(CH_2)_tOC_{1-6}$alkyl, optionally substituted $(CH_2)_tOC(=O)C_{1-6}$alkyl, optionally substituted $(CH_2)_tSC_{1-6}$alkyl, optionally substituted $(CH_2)_tOC(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl and optionally substituted $(CH_2)_tNR^aR^b$;

t is selected from 1, 2, 3, 4, 5 and 6 preferably 1, 2 or 3;

R^a and R^b are each independently selected from H or optionally substituted C_{1-6}alkyl;

or R_4 and R_5 together with the carbon atom to which they are attached form an optionally substituted 4-6-membered heterocyclic ring or C_{3-6}cycloalkyl ring; and

* represents the point of attachment to Ring A.

In one embodiment q is 0 or 1, preferably 0.

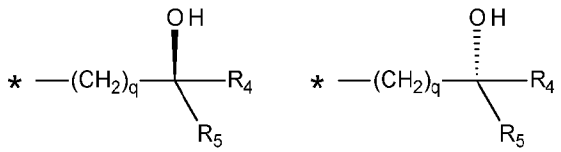
In one embodiment R_4 is H or optionally substituted C_{1-3}alkyl (particularly methyl and ethyl); and R_5 is selected from optionally substituted C_{1-3}alkyl (particularly methyl and ethyl), optionally substituted haloC_{1-3}alkyl (particularly CHF_2, CH_2CHF_2, CF_3 and CH_2CF_3), optionally substituted C_{3-7}cycloalkyl ring (particularly cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), optionally substituted 4-6-membered heterocyclyl ring (particularly morpholinyl), optionally substituted 5-6-membered heteroaryl ring (particularly containing at least one nitrogen heteroatom such as imidazolyl and pyridinyl); or R_4 and R_5 together with the carbon atom to which they are attached form an optionally substituted 4-6-membered heterocyclic ring or C_{3-6}cycloalkyl ring.

4-6-membered heterocyclic rings R_4 and R_5 together with the carbon atom to which they are attached include 4-membered rings such as oxetane and azetidine, 5-membered rings such as pyrrolidine, pyrazolidine, imidazole, tetrahydrofuran and thiophene and 6-membered rings such as piperidine, piperazine, morpholine, tetrahydropyran, and tetrahydrothiopyran. Heteroatom ring substituents in the case of heterocyclic rings include =O, e.g. S=O (e.g. to form oxo-thianes and dioxo-thianes from tetrahydrothiopyran), oxides e.g. N-oxides and C_{1-3}alkyl e.g. N-methyl.

C_{3-6}cycloalkyl rings R_4 and R_5 together with the carbon atom to which they are attached include saturated cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl rings, particularly cyclopentyl and cyclohexyl.

Suitable optional substituents for R_4 and R_5 may include but are not limited to, for example, one or more preferably 1 or 2 substituents independently selected from OH, C_{1-3}alkyl such as methyl, haloC_{1-3}alkyl such as CHF_2 and CF_3, CO_2H, CO_2C_{1-4}alkyl, C_{1-3}alkoxyl such as methoxy, oxo (=O), NH_2, NHC_{1-3}alkyl and $N(C_{1-3}alkyl)_2$.

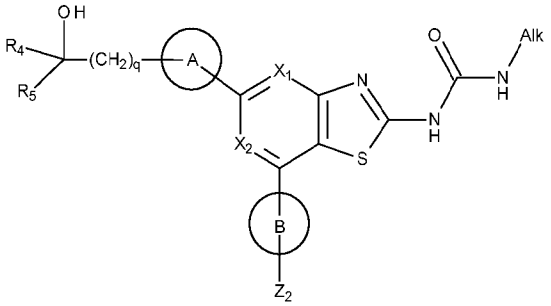
In a further embodiment Z_1 or Z_2, preferably Z_1, is a chiral alcohol of general formula



or an ester, carbamate, phosphate, sulfate or prodrug thereof wherein q, R_4, R_5 and * are as previously defined provided that R_4 and R_5 are different. In a preferred embodiment q is 0 or 1, preferably 0.

In one embodiment when Z_1 is a chiral alcohol, the compound of Formula (I) or (Ia) as previously defined may exist in the form of a racemic mixture, a single enantiomer and/or mixtures thereof.

In one embodiment the compound is of Formula (II):



(II)

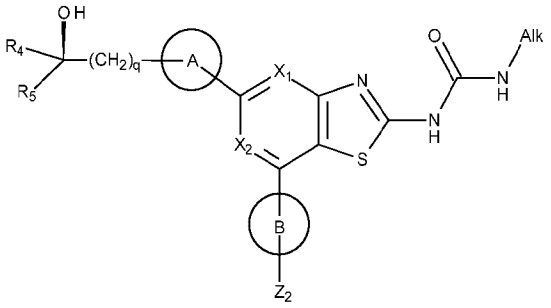
salts, racemates, diastereomers, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof

wherein X_1, X_2, Alk, Ring A, Ring B, Z_2, R_4, R_5 and q are as previously defined. In a preferred embodiment q is 0 or 1, preferably 0.

In a preferred embodiment X_1 is C-H, q is 0 or 1, preferably 0 and Alk is ethyl.

In still another embodiment, R_4 is H or optionally substituted C_{1-6}alkyl and R_5 is optionally substituted C_{1-6}alkyl. In a further more particular embodiment R_4 is H or an optionally substituted methyl, ethyl or propyl and R_5 is an optionally substituted methyl, ethyl or propyl.

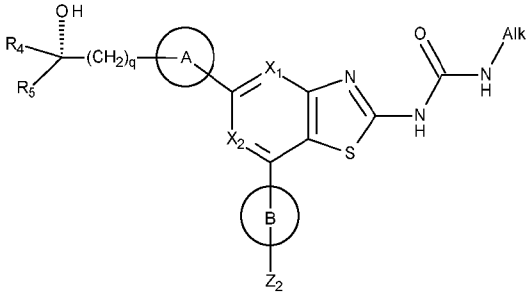
In one embodiment the compound of Formula (II) is in the form of a single enantiomer of Formula (IIa):



(IIa)

salts, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof wherein X_1, X_2, Alk, Ring A, Ring B, Z_2, R_4, R_5 and q are as previously defined provided that R_4 and R_5 are different. In a preferred embodiment q is 0 or 1, preferably 0.

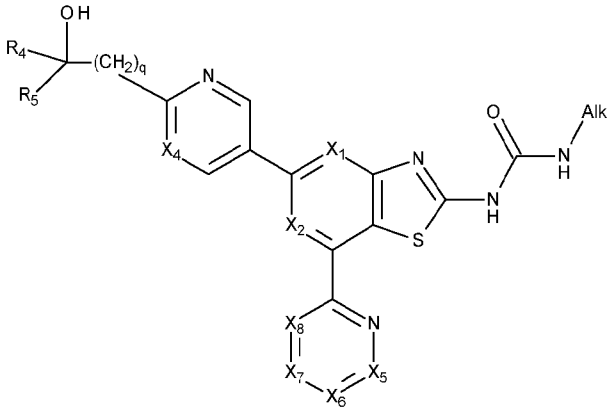
In another embodiment the compound of formula I is in the form of a single enantiomer of Formula (IIb):



(IIb)

salts, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof wherein X_1, X_2, Alk, Ring A, Ring B, Z_2, R_4, R_5 and q are as previously defined provided that R_4 and R_5 are different. In a preferred embodiment q is 0 or 1, preferably 0.

In one embodiment the compound is of Formula (III)



(III)

salts, racemates, diastereomers, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof

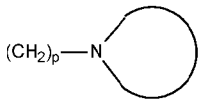
wherein X_1, X_2, Alk, R_4, R_5 and q are as previously defined;

X_4 is N, CH, C-halo or C-C_{1-3}alkoxy, preferably N or CH;

X_5, X_6, X_7 and X_8 are each independently selected from N, C-H or C-Z_2 where Z_2 is as previously defined provided that no more than one of X_5, X_6, X_7 or X_8 is N.

In a preferred embodiment X_1 is C-H, q is 0 or 1, preferably 0 and Alk is ethyl.

In one embodiment any one of X_5, X_6, X_7 or X_8 is C-Z_2 where Z_2 is selected from OH, optionally substituted C_{1-6}alkyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-6}$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl, optionally substituted $(CH_2)_mNR^aR^b$, optionally substituted $(CH_2)_p$-4-6-membered heterocyclic ring, optionally substituted $(CH_2)_p$-spiro-bicyclic-7-11-membered heterocyclic ring and optionally substituted



.

In one embodiment X_5, X_6, X_7 and X_8 are each independently C-H or C-Z_2.

In another embodiment one of X_5, X_6, X_7 and X_8 is N and each of the remainder independently selected from C-H or C-Z_2.

In still another embodiment, R_4 is H or optionally substituted C_{1-6}alkyl and R_5 is optionally substituted C_{1-6}alkyl. In a further more particular embodiment R_4 is H or an optionally substituted methyl, ethyl or propyl and R_5 is an optionally substituted methyl, ethyl or propyl.

In one embodiment of the compounds of any one of Formula (I), (Ia), (II), (IIa), (IIb) or (III), the Z_1 and/or Z_2 secondary or tertiary alcohol is in the form of an ester including those derived from amino acids and dipeptides, a carbamate, a phosphate or sulphate.

In one embodiment of the compounds of any one of Formula (I), (Ia), (II), (IIa), (IIb) or (III), the ester of the Z_1 and/or Z_2 secondary or tertiary alcohol is of general formula $OC(=O)R_6$ where R_6 is a 5-6-membered heterocycle or an optionally substituted C_{1-6}alkyl wherein the optional substituents are independently selected from 1, 2, 3 or 4 moieties selected from C_{1-3}alkyl, C_{1-3}alkoxyl, OH, OC_{1-3}alkyl, CO_2H, CO_2C_{1-3}alkyl, optionally substituted 5-6-membered heterocycles, $NHC(O)C_{1-6}$alkyl, NHC(O)-5-6-membered heterocycles, $C(O)NHC_{1-6}$alkyl, NH_2, NHC_{1-3}alkyl and $N(C_{1-3}alkyl)_2$ wherein $NHC(O)C_{1-6}$alkyl, $C(O)NHC_{1-6}$alkyl, NHC_{1-3}alkyl and $N(C_{1-3}alkyl)_2$ may be further optionally substituted with, for example, CO_2H, CO_2CH_3, a 5-6-membered heterocycle, NH_2, NHC_{1-3}alkyl and $N(C_{1-3}alkyl)_2$ and $OP(=O)(OR_9)_2$ where each R_9 is indenpendently selected from H or C_{1-3}alkyl. Preferred 5-6 membered heterocycles include optionally substituted morpholino and optionally substituted pyrrolidine, pyrazolidine, imidazoline, piperidine and piperazine (such as N-methyl piperazine). In a particular embodiment there is provided a succinate ester of the Z_1 and/or Z_2 secondary or tertiary alcohol.

In another embodiment there is provided an ester of the Z_1 and/or Z_2 secondary or tertiary alcohol wherein the ester is derived from an amino acid or a dipeptide moiety.

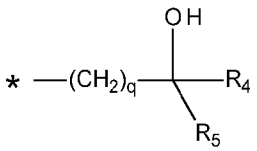
In one embodiment of the compounds of any one of Formula (I), (Ia), (II), (IIa), (IIb) or (III), the carbamate of the Z_1 and/or Z_2 secondary or tertiary alcohol is of general formula $OC(=O)NR_7R_8$ where R_7 and R_8 are each independently selected from H and optionally substituted C_{1-6}alkyl or join together with the N to which they are attached to form an optionally substituted 5-6-membered heterocycle. Preferred 5-6 membered heterocycle include optionally substituted morpholino and optionally substituted pyrrolidine, pyrazolidine, imidazoline, piperidine and piperazine (such as N-methyl piperazine).

In another embodiment of the compounds of any one of Formula (I), (Ia), (II), (IIa), (IIb) or (III), the phosphate of the Z_1 and/or Z_2 secondary or tertiary alcohol is of general formula $OP(O)(OR_9)_2$ where each R_9 is independently selected from H or an optionally substituted C_{1-6}alkyl.

In still another embodiment of the compounds of any one of Formula (I), (Ia), (II), (IIa), (IIb) or (III), the sulphate of the Z_1 and/or Z_2 secondary or tertiary alcohol is of general formula OSO_2OR_{10} where R_{10} is H or an optionally substituted C_{1-6}alkyl.

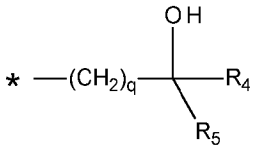
In one embodiment of the compounds of any one of Formula (I), (Ia), (II), (IIa), (IIb) or (III), the prodrug is selected from an ester, carbamate, phosphate or sulphate formed from the hydroxyl moiety of the secondary or tertiary alcohol as previously defined.

In a particularly preferred embodiment of the compounds of any one of Formula (I), (Ia), (II), (IIa), (IIb) or (III), Z_1 is a secondary or tertiary alcohol of general formula



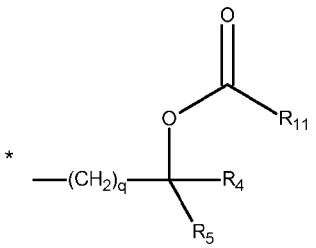
or an ester or phosphate thereof as previously defined.

Accordingly, in one embodiment of the compounds of any one of Formula (I), (Ia), (II), (IIa), (IIb) or (III) there is provided an ester of the Z_1 secondary or tertiary alcohol of general formula:



wherein the ester is derived from an amino acid, a dipeptide, a carbamate, a phosphate or a sulphate.

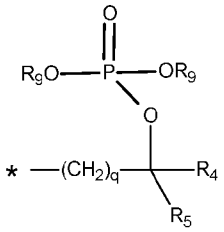
In one embodiment of the compounds of any one of Formula (I), (Ia), (II), (IIa), (IIb) or (III) there is provided an ester of the Z_1 secondary or tertiary alcohol of general formula:



wherein R_{11} is R_6 or NR_7R_8 and wherein R_6, R_7, R_8, q, R_4 and R_5 are as previously defined. In one embodiment, R_{11} is selected from the group consisting of an

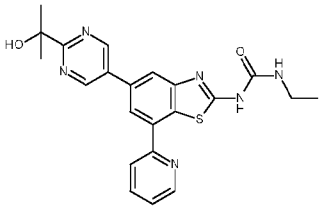
optionally substituted 5-6-membered heterocyclyl or an optionally substituted C_{1-6}alkyl. Particularly preferred 5-6-membered heterocyclyl include pyrrolidinyl, morpholinyl and piperazinyl and may be optionally substituted with C_{1-3}alkyl, preferablyl methyl. In one embodiment R_{11} is an optionally substituted C_{1-6}alkyl wherein particularly preferred optional substituents are independently selected from methyl, methoxy, OH, CO_2H, CO_2C_{1-3}alkyl (particularly CO_2CH_3), optionally substituted 5-6-membered heterocycles, NHC(=O)- 5-6-membered heterocycles, NH_2, NHC_{1-3}alkyl and $N(C_{1-3}alkyl)_2$ (particularly $N(CH_3)_2$) and wherein NHC_{1-3}alkyl may be further optionally substituted with NH_2, CO_2H, CO_2CH_3, 5-6-membered heterocyclyls and $OP(=O)(OR_9)_2$ where each R_9 is indenpendently selected from H or C_{1-3}alkyl and wherein particularly preferred 5-6-membered heterocycles include pyrrolidinyl, piperazinyl and morpholinyl.

In yet another embodiment of the compounds of any one of Formula (I), (Ia), (II), (IIa), (IIb) or (III) there is provided a phosphate of the Z_1 secondary or tertiary alcohol of general formula:

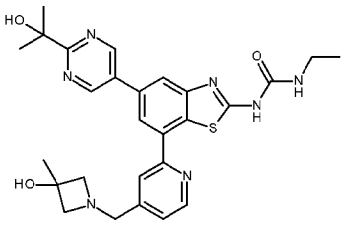


wherein each R_9 is independently selected from H or an optionally substituted C_{1-3}alkyl and q, R_4 and R_5 are as previously defined. In one embodiment each R_9 is H.

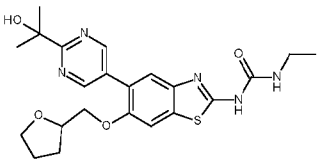
In one embodiment the compound is selected from the group consisting of any one of compounds 1 to 202:



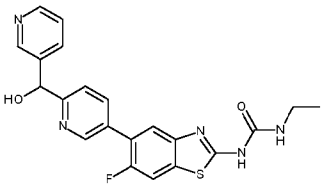
1;



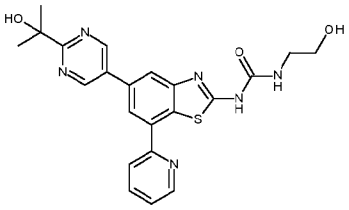
2;



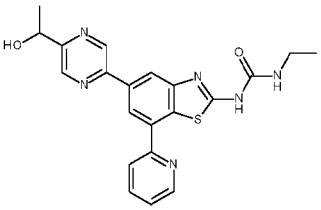
3;



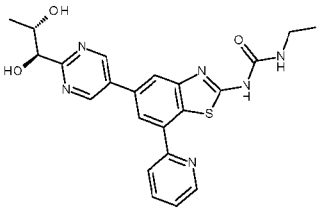
4;



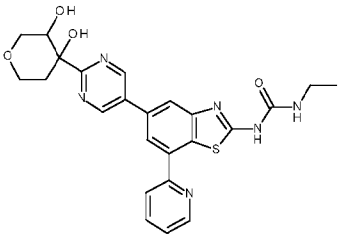
5;



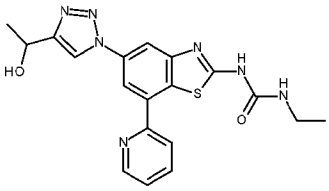
6;



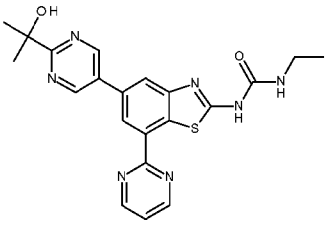
(mixture trans-diol)
7;



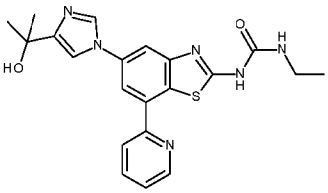
8;



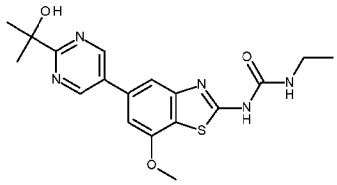
9;



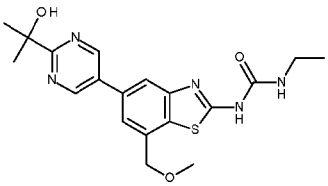
10;



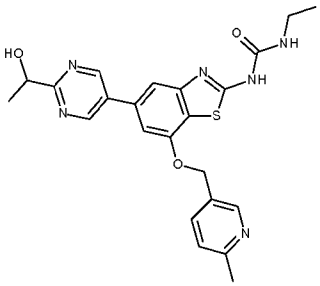
11;



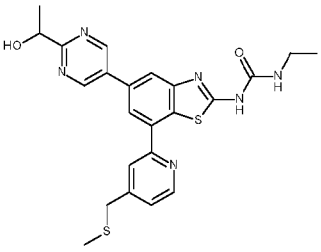
12;



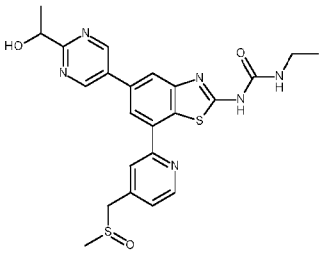
13;



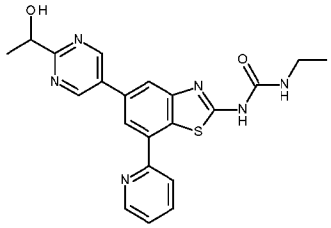
14;



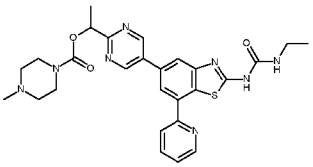
15;



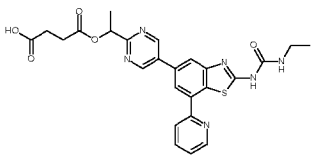
16;



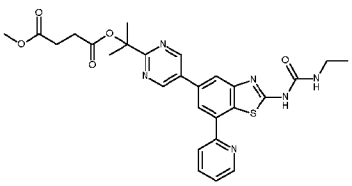
17;



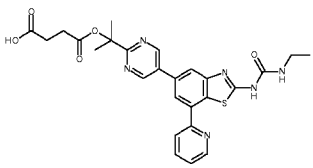
18;



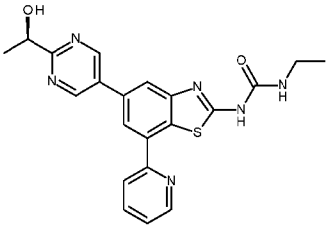
19;



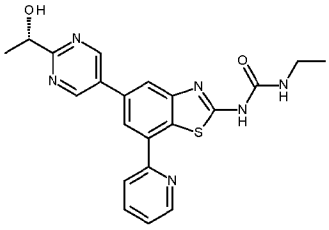
20;



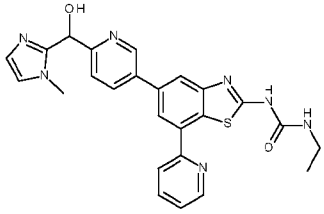
21;



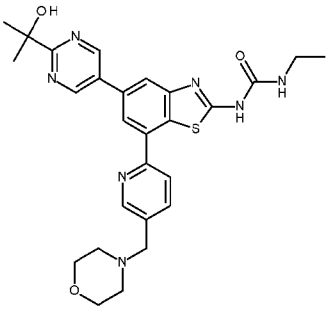
22;



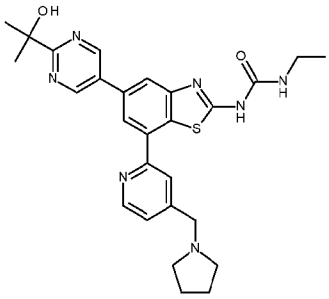
23;



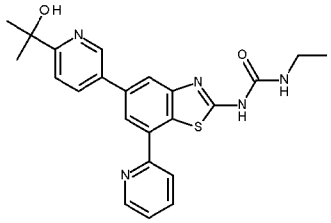
24;



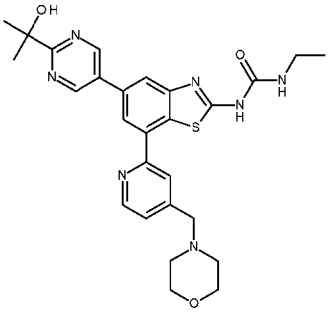
25;



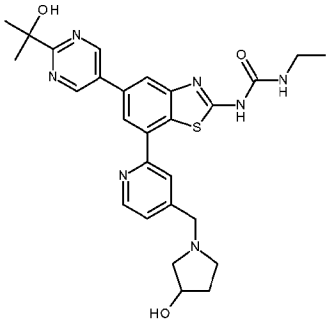
26;



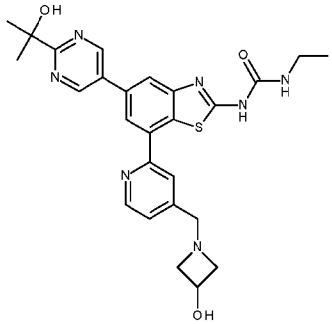
27;



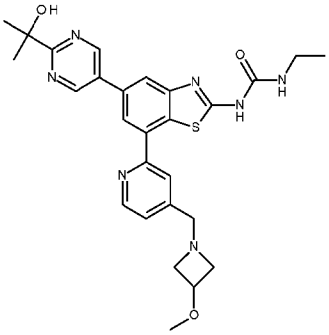
28;



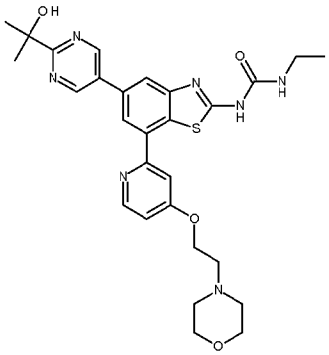
29;



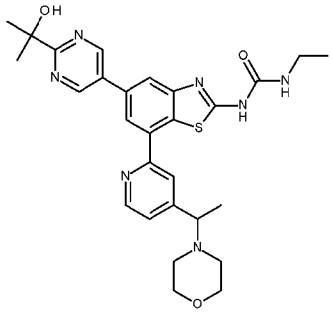
30;



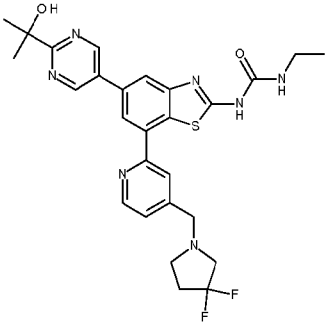
31;

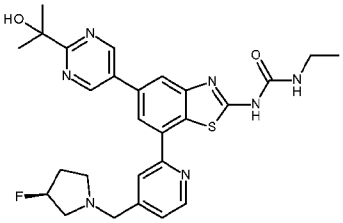


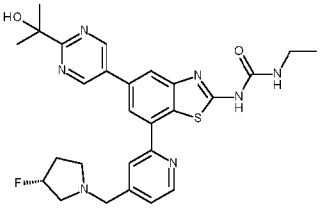
32;



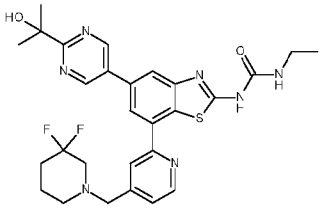
33;



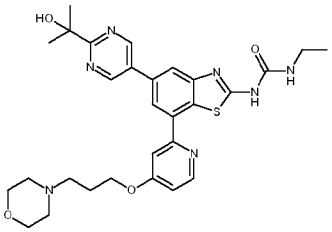




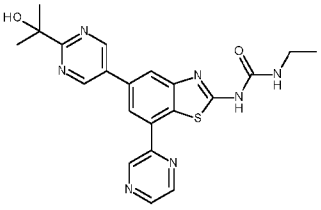
34;



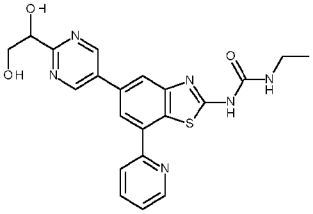
35;



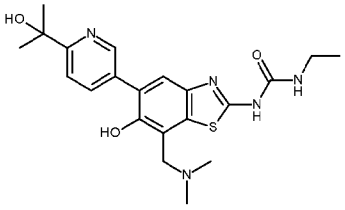
36;



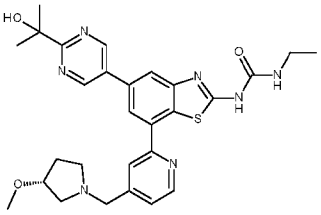
37;



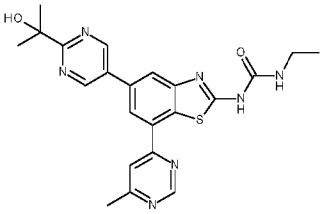
38;



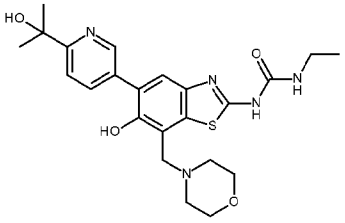
39;



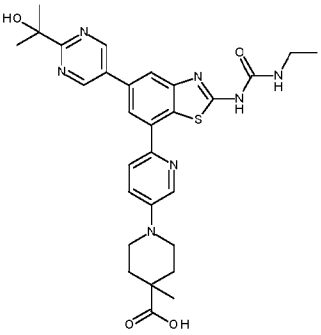
40;



41;



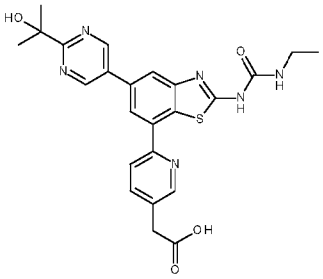
42;



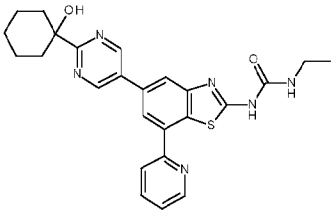
43;

44;

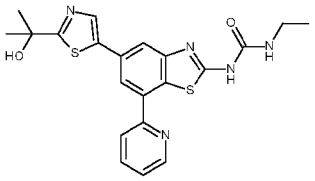
45;



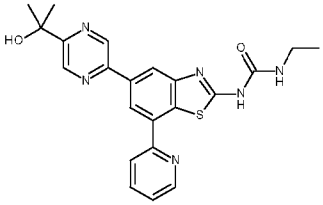
46;



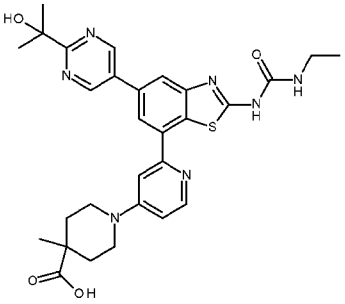
47;



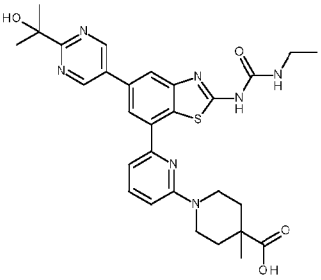
48;



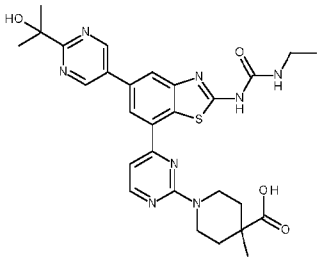
49;



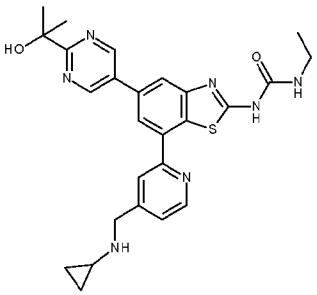
50;



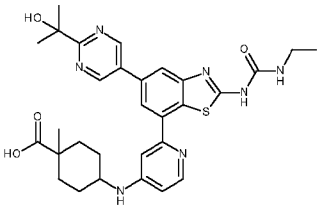
51;



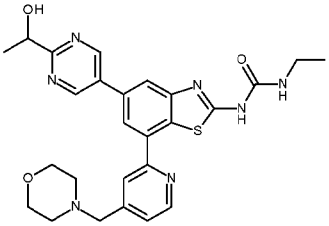
52;



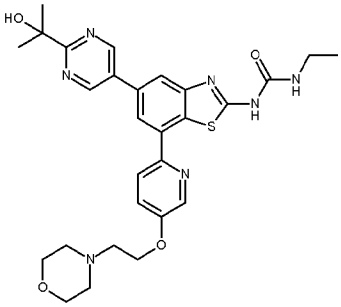
53;



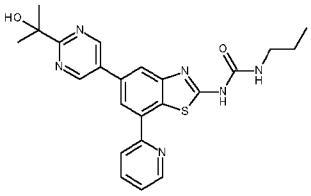
54;



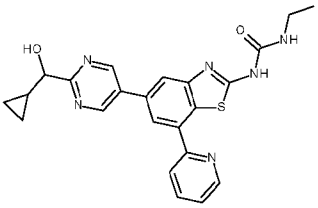
55;



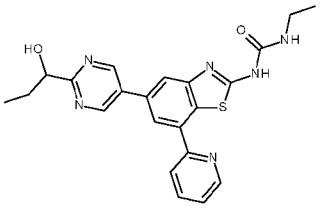
56;



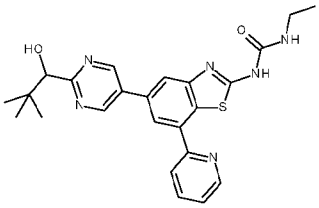
57;



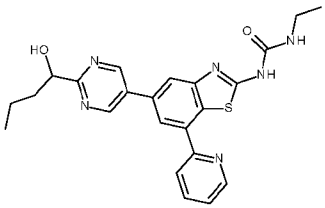
58;



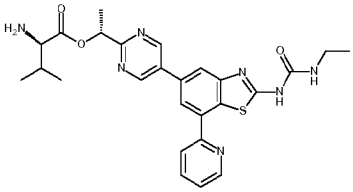
59;



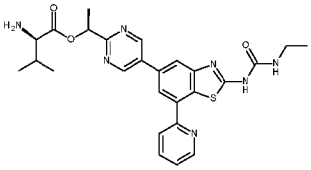
60;



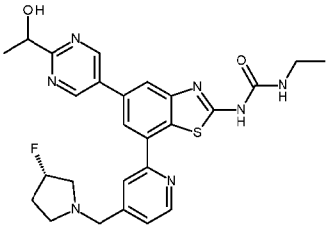
61;



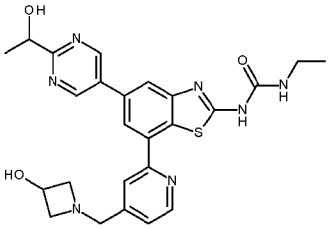
62;



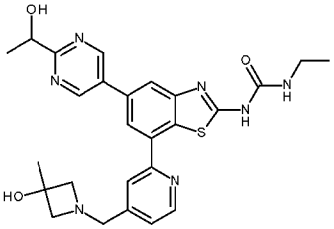
63;



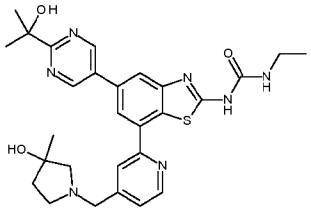
64;



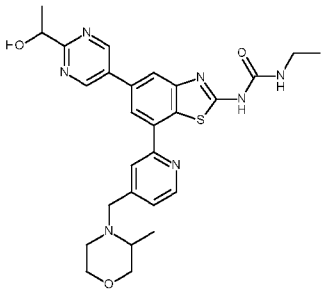
65;



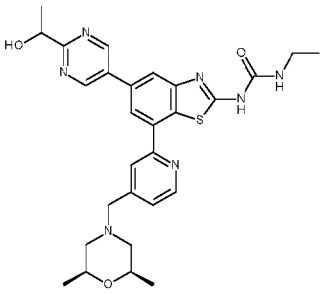
66;



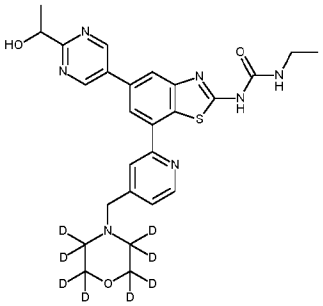
67;



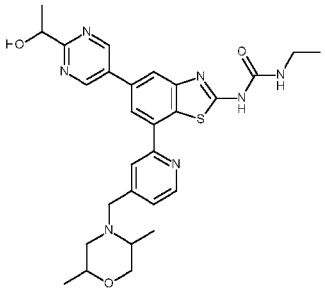
68;



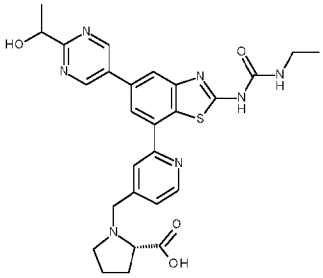
69;



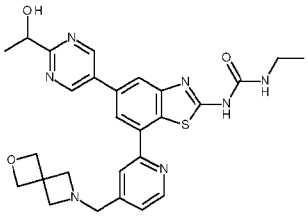
70;



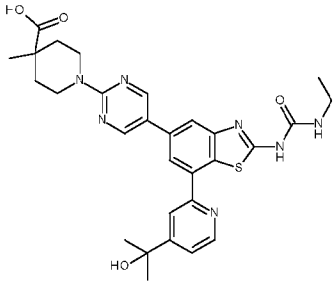
71;



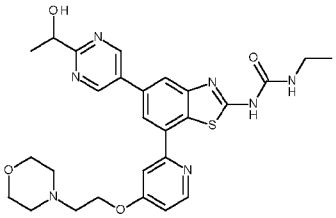
72;



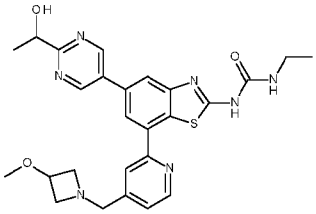
73;



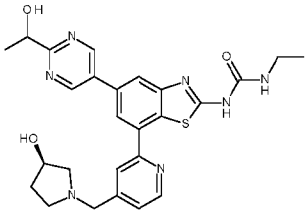
74;



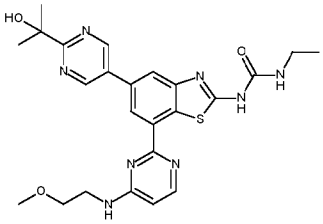
75;



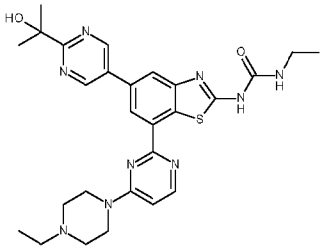
76;



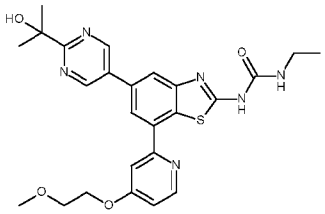
77;



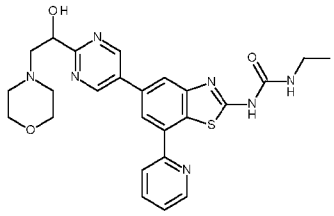
78;



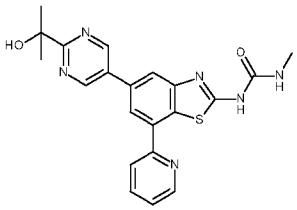
79;



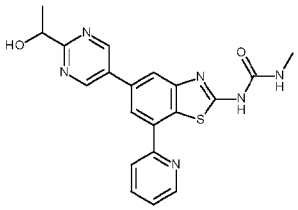
80;



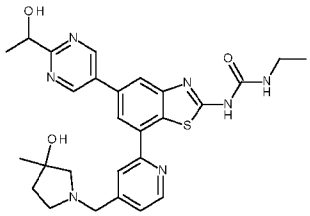
81;



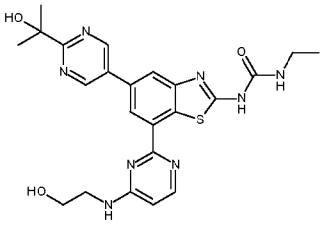
82;



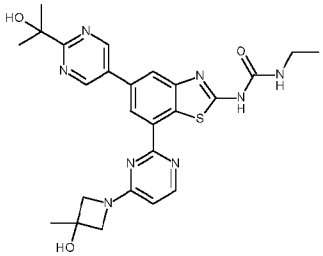
83;



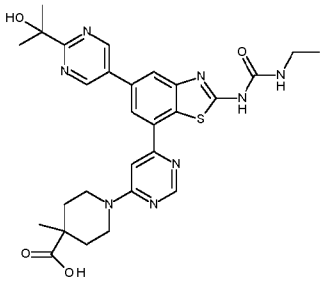
84;



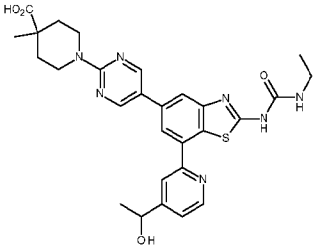
85;



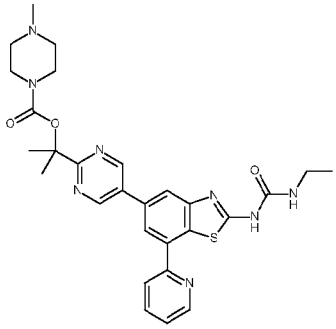
86;



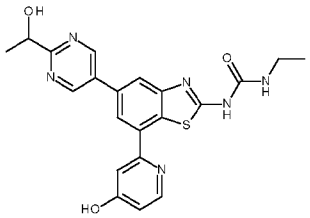
87;



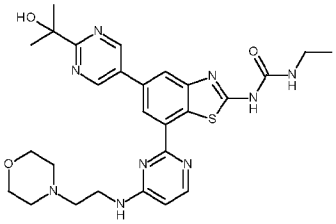
88;



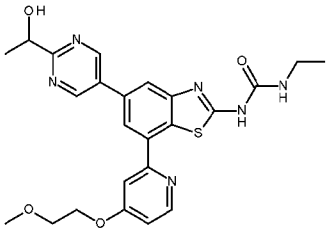
89;



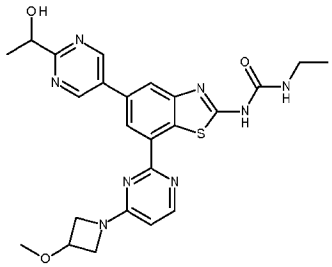
90;



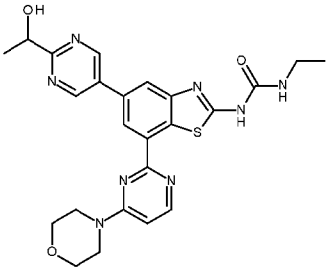
91;



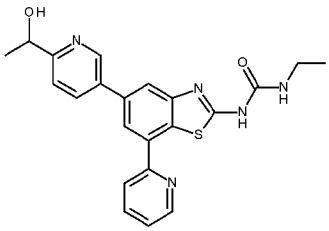
92;



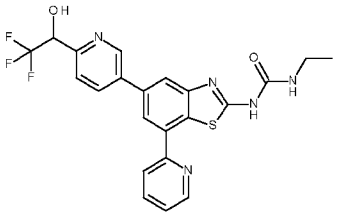
93;



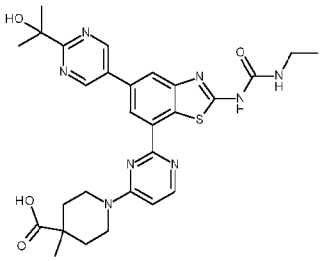
94;



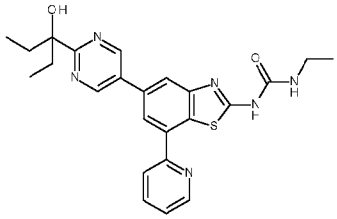
95;



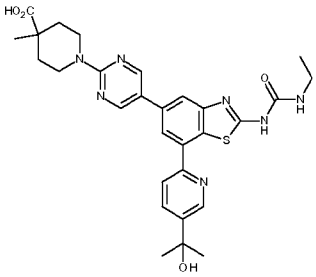
96;



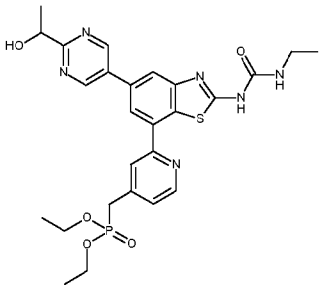
97;



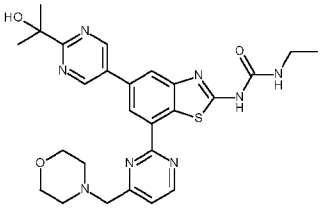
98;



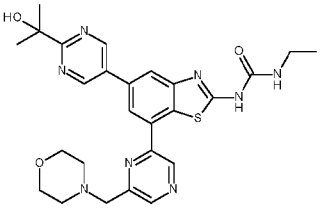
99;



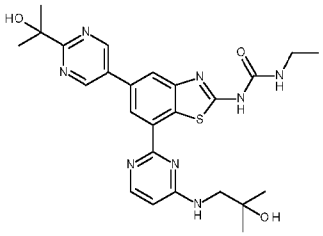
100;



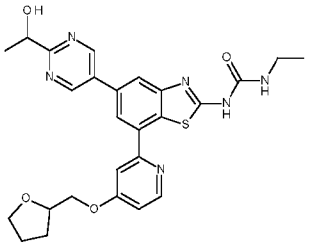
101;



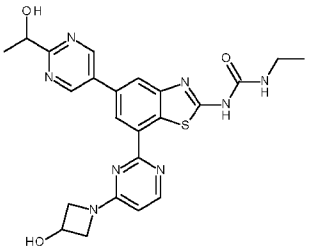
102;



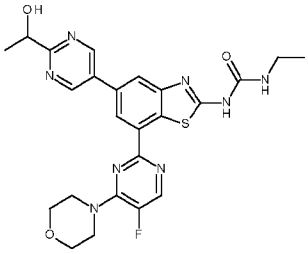
103;



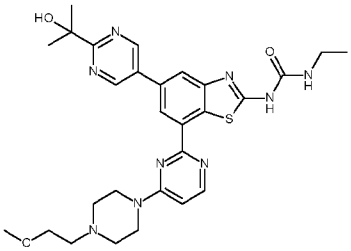
104;



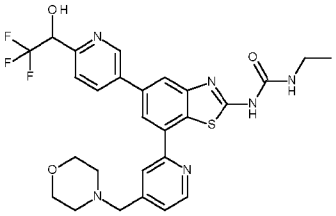
105;



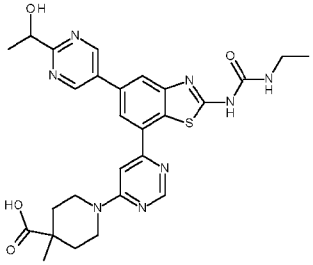
106;



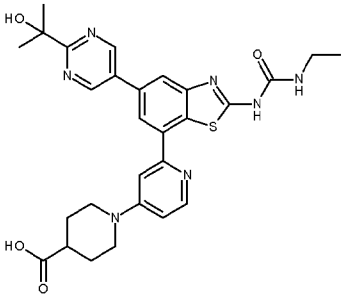
107;



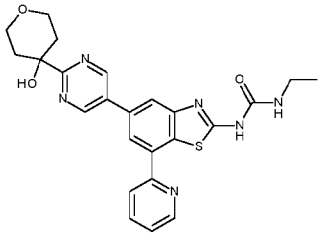
108;



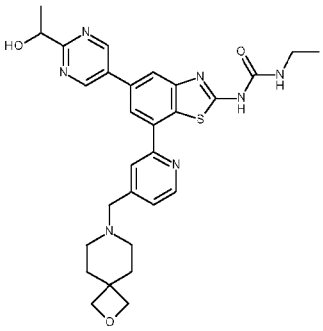
109;



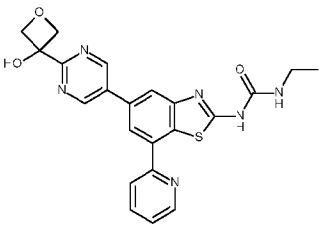
110;



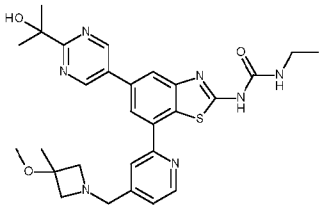
111;



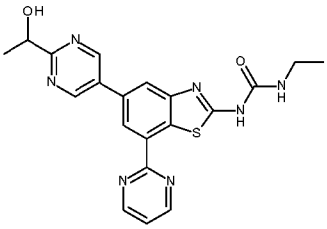
112;



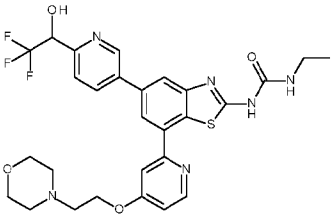
113;



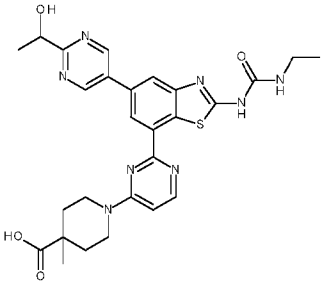
114;



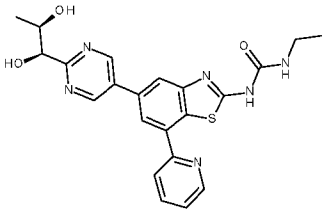
115;



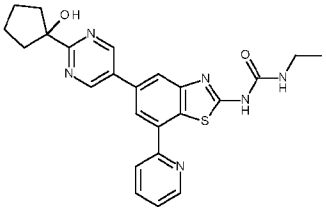
116;



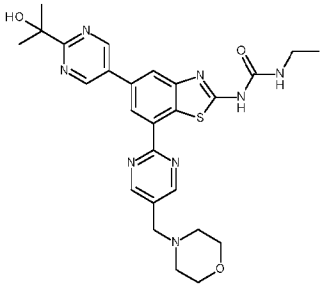
117;



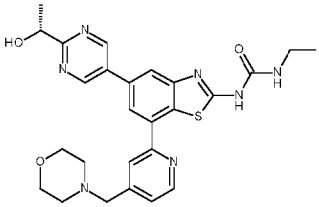
(mixture cis-diols)
118;



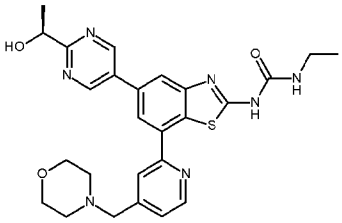
119;



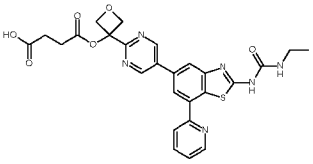
120;



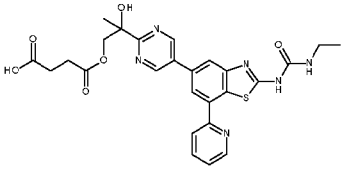
121;



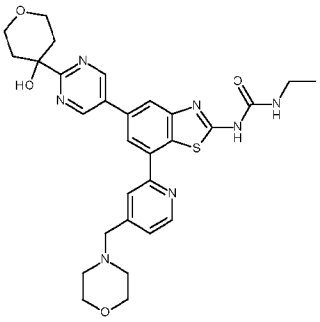
122;



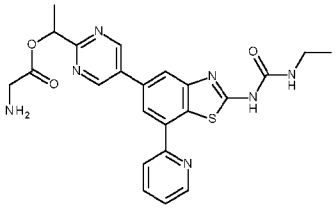
123;



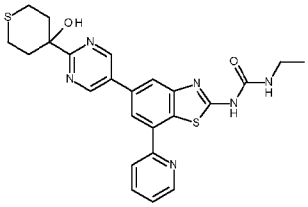
124;



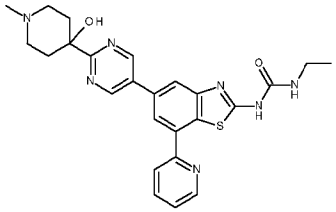
125;



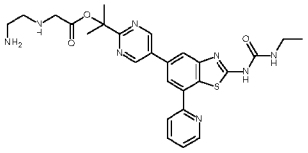
126;



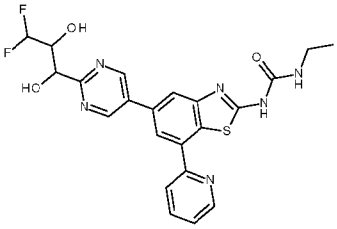
127;



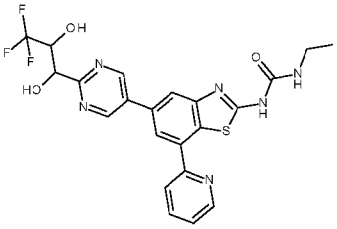
128;



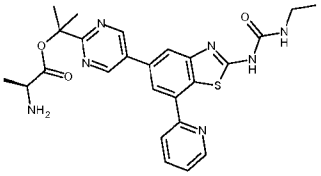
129;



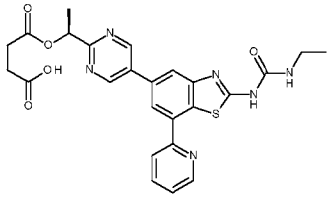
130;



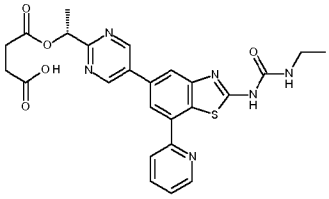
131;



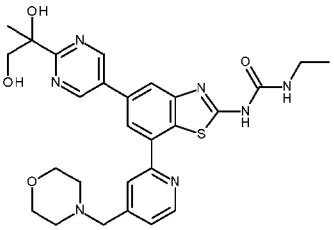
132;



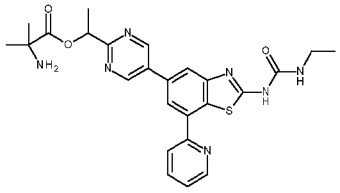
133;



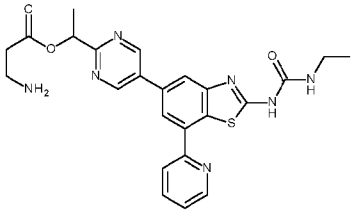
134;



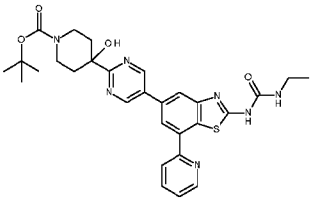
135;



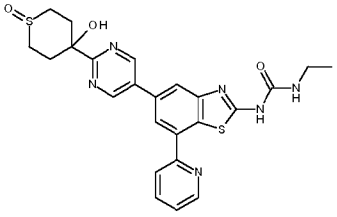
136;



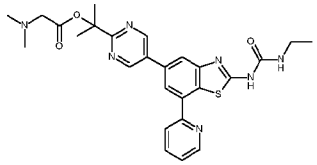
137;



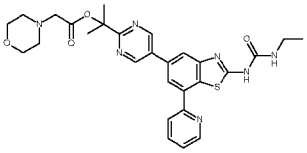
138;



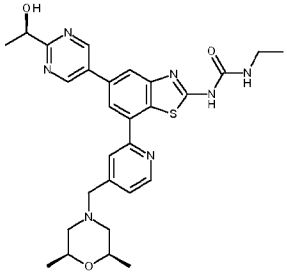
139;



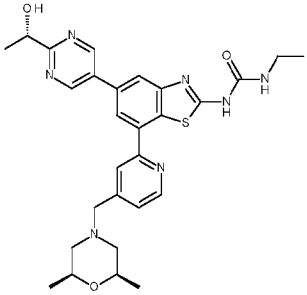
140;



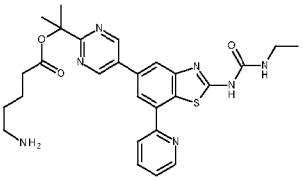
141;



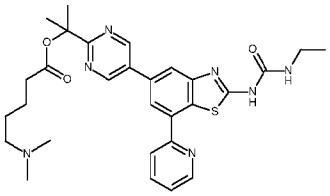
142;



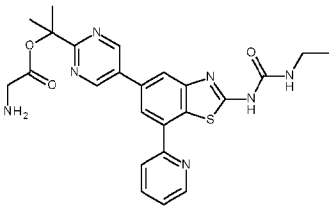
143;



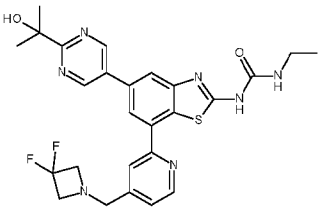
144;



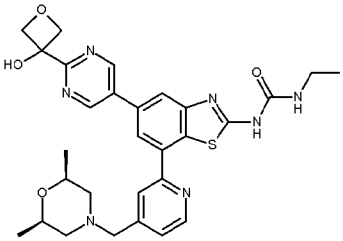
145;



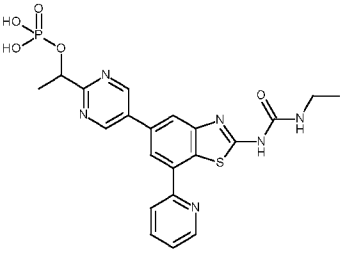
146;



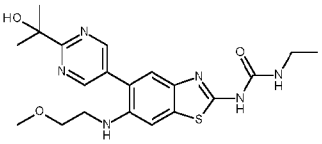
147;



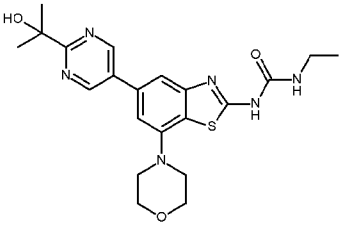
148;



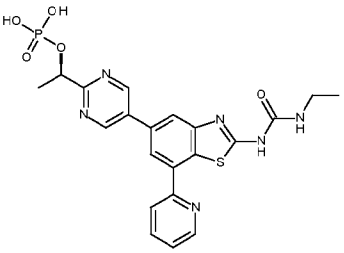
149;



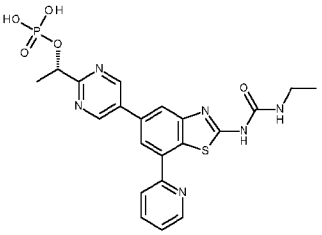
150;



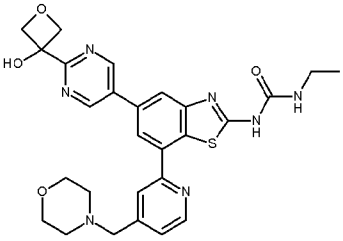
151;



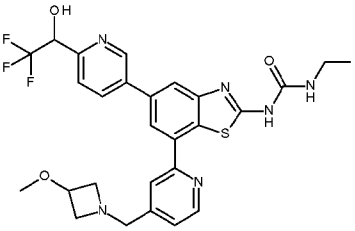
152;



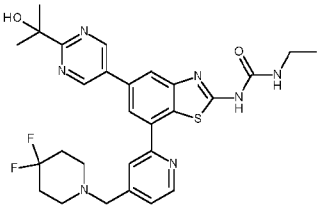
153;



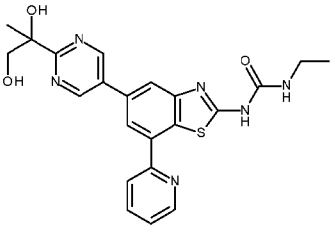
154;



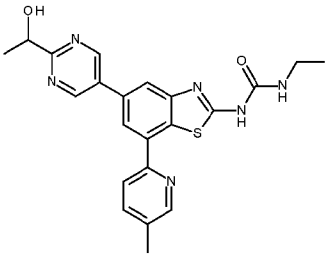
155;



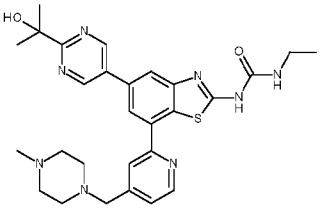
156;



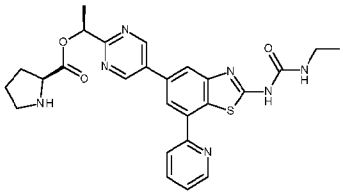
157;



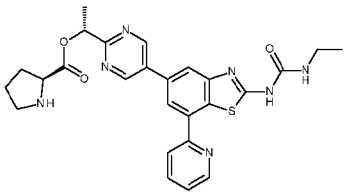
158;



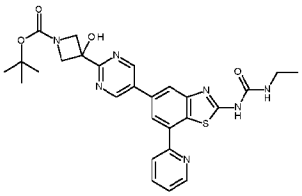
159;



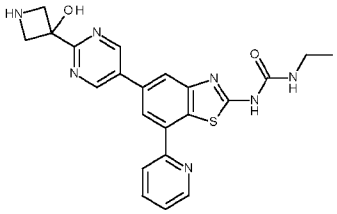
160;



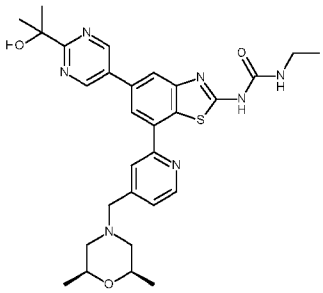
161;



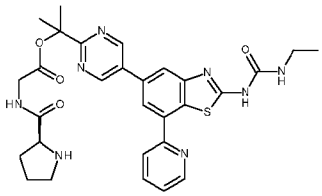
162;



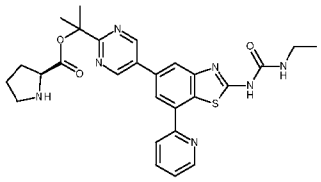
163;



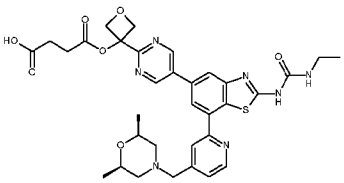
164;



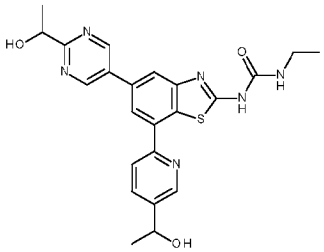
165;



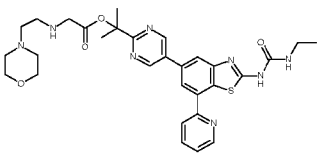
166;



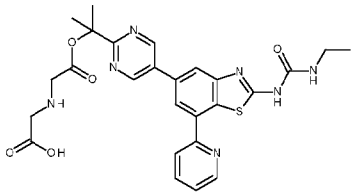
167;



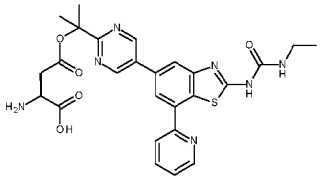
168;



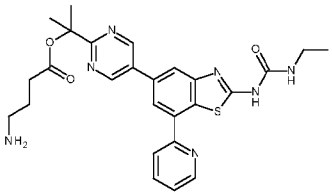
169;



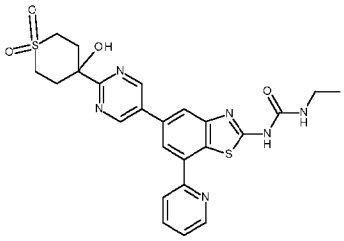
170;



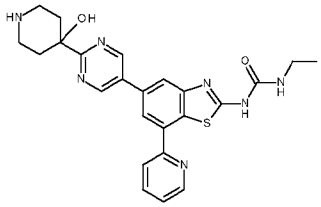
171;



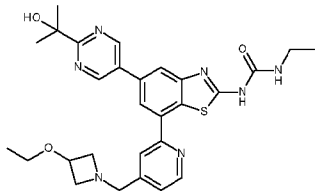
172;



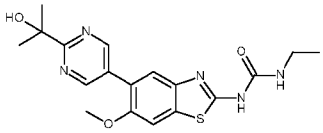
173;



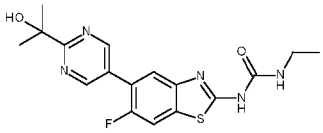
174;



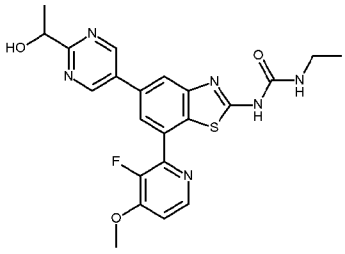
175;



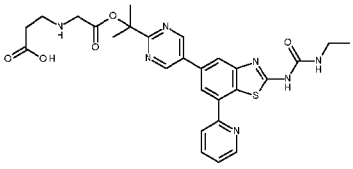
176;



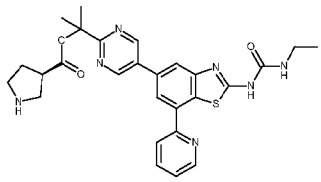
177;



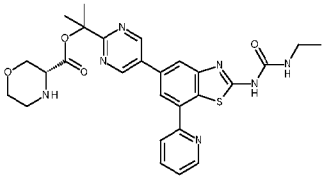
178;



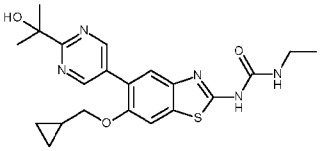
179;



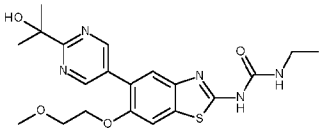
180;



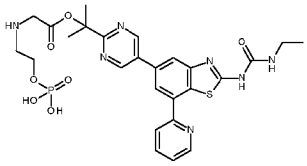
181;



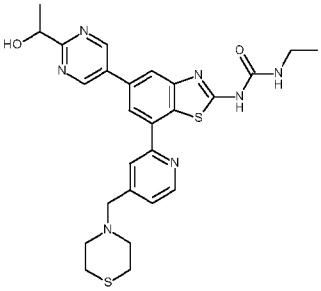
182;



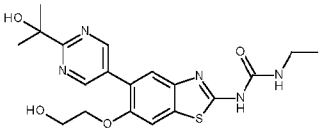
183;



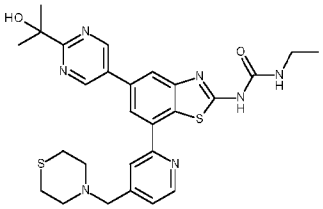
184;



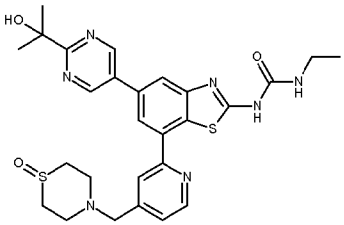
185;



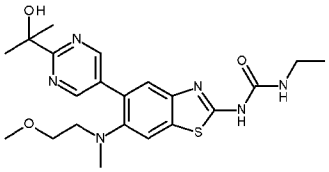
186;



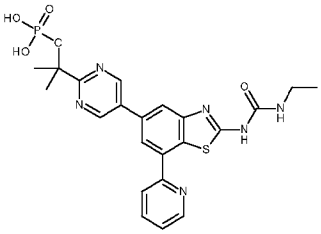
187;



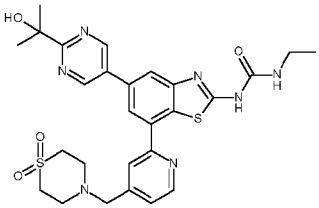
188;



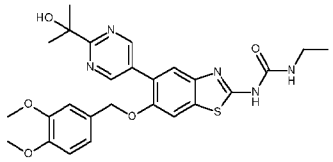
189;



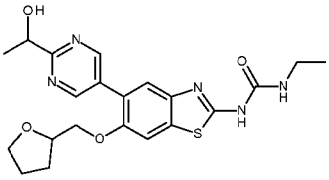
190;



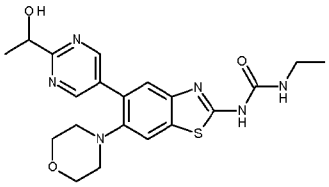
191;



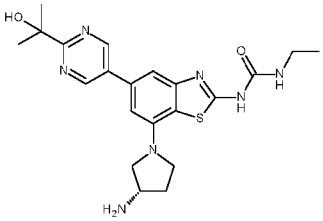
192;



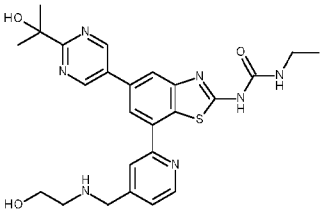
193;



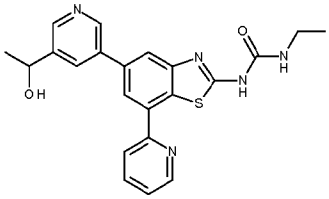
194;



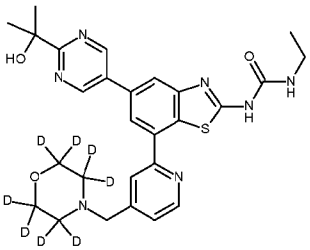
195;



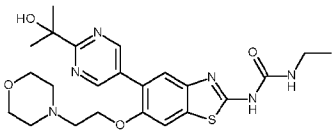
196;



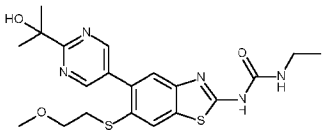
197;



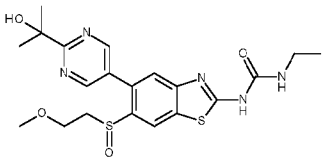
198;



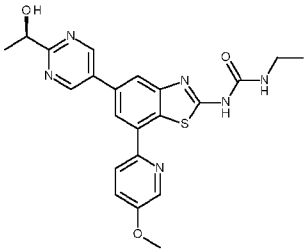
199;



200;



201; and



202;

salts, racemates, diastereomers, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof wherein compounds 1 to 202 are named as follows:

1) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;
2) 1-ethyl-3-[7-[4-[(3-hydroxy-3-methyl-azetidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;
3) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(tetrahydrofuran-2-ylmethoxy)-1,3-benzothiazol-2-yl]urea;
4) 1-ethyl-3-[6-fluoro-5-[6-[hydroxy(3-pyridyl)methyl]-3-pyridyl]-1,3-benzothiazol-2-yl]urea;
5) 1-(2-hydroxyethyl)-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;
6) 1-ethyl-3-[5-[5-(1-hydroxyethyl)pyrazin-2-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;
7) 1-[5-[2-[(1S*,2R*)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (mixture 1-[5-[2-[(1S,2R)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea; and 1-[5-[2-[(1R,2S)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea);

8) 1-[5-[2-[(3R*,4S*)-3,4-dihydroxytetrahydropyran-4-yl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (mixture 1-[5-[2-[(3R,4S)-3,4-dihydroxytetrahydropyran-4-yl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea; and 1-[5-[2-[(3S,4R)-3,4-dihydroxytetrahydropyran-4-yl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea);

9) 1-ethyl-3-[5-[4-(1-hydroxyethyl)triazol-1-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

10) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-pyrimidin-2-yl-1,3-benzothiazol-2-yl]urea;

11) 1-ethyl-3-[5-[4-(1-hydroxy-1-methyl-ethyl)imidazol-1-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

12) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-methoxy-1,3-benzothiazol-2-yl]urea;

13) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(methoxymethyl)-1,3-benzothiazol-2-yl]urea;

14) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[(6-methyl-3-pyridyl)methoxy]-1,3-benzothiazol-2-yl]urea;

15) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(methylsulfanylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

16) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(methylsulfinylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

17) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

18) 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl 4-methylpiperazine-1-carboxylate;

19) 4-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethoxy]-4-oxo-butanoic acid;

20) O4-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] O1-methyl butanedioate;

21) 4-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethoxy]-4-oxo-butanoic acid;

22) 1-ethyl-3-[5-[2-[(1R)-1-hydroxyethyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

23) 1-ethyl-3-[5-[2-[(1S)-1-hydroxyethyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

24) 1-ethyl-3-[5-[6-[hydroxy-(1-methylimidazol-2-yl)methyl]-3-pyridyl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

25) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[5-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

26) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(pyrrolidin-1-ylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

27) 1-ethyl-3-[5-[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

28) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

29) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(3-hydroxypyrrolidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

30) 1-ethyl-3-[7-[4-[(3-hydroxyazetidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

31) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(3-methoxyazetidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

32) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(2-morpholinoethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

33) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(1-morpholinoethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

34) 1-[7-[4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

35) 1-ethyl-3-[7-[4-[[(3S)-3-fluoropyrrolidin-1-yl]methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

36) 1-ethyl-3-[7-[4-[[(3R)-3-fluoropyrrolidin-1-yl]methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

37) 1-[7-[4-[(3,3-difluoro-1-piperidyl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

38) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(3-morpholinopropoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

39) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-pyrazin-2-yl-1,3-benzothiazol-2-yl]urea;

40) 1-[5-[2-(1,2-dihydroxyethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea;

41) 1-[7-(dimethylaminomethyl)-6-hydroxy-5-[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

42) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[[(3R)-3-methoxypyrrolidin-1-yl]methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

43) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(6-methylpyrimidin-4-yl)-1,3-benzothiazol-2-yl]urea;

44) 1-ethyl-3-[6-hydroxy-5-[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]-7-(morpholinomethyl)-1,3-benzothiazol-2-yl]urea;

45) 1-[6-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-3-pyridyl]-4-methyl-piperidine-4-carboxylic acid;

46) 2-[6-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-3-pyridyl]acetic acid;

47) 1-ethyl-3-[5-[2-(1-hydroxycyclohexyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

48) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)thiazol-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

49) 1-ethyl-3-[5-[5-(1-hydroxy-1-methyl-ethyl)pyrazin-2-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

50) 1-[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-4-pyridyl]-4-methyl-piperidine-4-carboxylic acid;

51) 1-[6-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-2-pyridyl]-4-methyl-piperidine-4-carboxylic acid;

52) 1-[4-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]pyrimidin-2-yl]-4-methyl-piperidine-4-carboxylic acid;

53) 1-[7-[4-[(cyclopropylamino)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

54) 4-[[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-4-pyridyl]amino]-1-methyl-cyclohexanecarboxylic

acid;

55) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

56) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[5-(2-morpholinoethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

57) 1-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-propyl-urea;

58) 1-[5-[2-[cyclopropyl(hydroxy)methyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea;

59) 1-ethyl-3-[5-[2-(1-hydroxypropyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

60) 1-ethyl-3-[5-[2-(1-hydroxy-2,2-dimethyl-propyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

61) 1-ethyl-3-[5-[2-(1-hydroxybutyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea

62) [(1R)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] (2R)-2-amino-3-methyl-butanoate;

63) [(1S)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] (2R)-2-amino-3-methyl-butanoate;

64) 1-ethyl-3-[7-[4-[[(3S)-3-fluoropyrrolidin-1-yl]methyl]-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

65) 1-ethyl-3-[7-[4-[(3-hydroxyazetidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

66) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[(3-hydroxy-3-methyl-azetidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

67) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(3-hydroxy-3-methyl-pyrrolidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

68) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[(3-methylmorpholin-4-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

69) 1-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

70) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

71) 1-[7-[4-[(2,5-dimethylmorpholin-4-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

72) (2S)-1-[[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-4-pyridyl]methyl]pyrrolidine-2-carboxylic acid;

73) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(6-oxa-2-azaspiro[3.3]heptan-2-ylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

74) 1-[5-[2-(ethylcarbamoylamino)-7-[4-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-4-methyl-piperidine-4-carboxylic acid;

75) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(2-morpholinoethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

76) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[(3-methoxyazetidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

77) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[[(3R)-3-hydroxypyrrolidin-1-yl]methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

78) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(2-methoxyethylamino)pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

79) 1-ethyl-3-[7-[4-(4-ethylpiperazin-1-yl)pyrimidin-2-yl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

80) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(2-methoxyethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

81) 1-ethyl-3-[5-[2-(1-hydroxy-2-morpholino-ethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

82) 1-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-methyl-urea;

83) 1-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-methyl-urea;

84) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[(3-hydroxy-3-methyl-pyrrolidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

85) 1-ethyl-3-[7-[4-(2-hydroxyethylamino)pyrimidin-2-yl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

86) 1-ethyl-3-[7-[4-(3-hydroxy-3-methyl-azetidin-1-yl)pyrimidin-2-yl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

87) 1-[6-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]pyrimidin-4-yl]-4-methyl-piperidine-4-carboxylic acid;

88) 1-[5-[2-(ethylcarbamoylamino)-7-[4-(1-hydroxyethyl)-2-pyridyl]-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-4-methyl-piperidine-4-carboxylic acid;

89) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 4-methylpiperazine-1-carboxylate;

90) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-(4-hydroxy-2-pyridyl)-1,3-benzothiazol-2-yl]urea;

91) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(2-morpholinoethylamino)pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

92) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(2-methoxyethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

93) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(3-methoxyazetidin-1-yl)pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

94) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-(4-morpholinopyrimidin-2-yl)-1,3-benzothiazol-2-yl]urea;

95) 1-ethyl-3-[5-[6-(1-hydroxyethyl)-3-pyridyl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

96) 1-ethyl-3-[7-(2-pyridyl)-5-[6-(2,2,2-trifluoro-1-hydroxy-ethyl)-3-pyridyl]-1,3-benzothiazol-2-yl]urea;

97) 1-[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]pyrimidin-4-yl]-4-methyl-piperidine-4-carboxylic acid;

98) 1-ethyl-3-[5-[2-(1-ethyl-1-hydroxy-propyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

99) 1-[5-[2-(ethylcarbamoylamino)-7-[5-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-4-methyl-piperidine-4-carboxylic acid;

100) 1-[7-[4-(diethoxyphosphorylmethyl)-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

101) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

102) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[6-(morpholinomethyl)pyrazin-2-yl]-1,3-benzothiazol-2-yl]urea;

103) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(2-hydroxy-2-methyl-propyl)amino]pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

104) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(tetrahydrofuran-2-ylmethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

105) 1-ethyl-3-[7-[4-(3-hydroxyazetidin-1-yl)pyrimidin-2-yl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

106) 1-ethyl-3-[7-(5-fluoro-4-morpholino-pyrimidin-2-yl)-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

107) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

108) 1-ethyl-3-[7-[4-(morpholinomethyl)-2-pyridyl]-5-[6-(2,2,2-trifluoro-1-hydroxy-ethyl)-3-pyridyl]-1,3-benzothiazol-2-yl]urea;

109) 1-[6-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]pyrimidin-4-yl]-4-methyl-piperidine-4-carboxylic acid;

110) 1-[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-4-pyridyl]piperidine-4-carboxylic acid;

111) 1-ethyl-3-[5-[2-(4-hydroxytetrahydropyran-4-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

112) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(2-oxa-7-azaspiro[3.5]nonan-7-ylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

113) 1-ethyl-3-[5-[2-(3-hydroxyoxetan-3-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

114) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(3-methoxy-3-methyl-azetidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

115) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-pyrimidin-2-yl-1,3-benzothiazol-2-yl]urea;

116) 1-ethyl-3-[7-[4-(2-morpholinoethoxy)-2-pyridyl]-5-[6-(2,2,2-trifluoro-1-hydroxy-ethyl)-3-pyridyl]-1,3-benzothiazol-2-yl]urea;

117) 1-[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]pyrimidin-4-yl]-4-methyl-piperidine-4-carboxylic acid;

118) 1-[5-[2-[(1R*,2R*)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (mixture 1-[5-[2-[(1R,2R)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea; and 1-[5-[2-[(1S,2S)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea);

119) 1-ethyl-3-[5-[2-(1-hydroxycyclopentyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

120) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[5-(morpholinomethyl)pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

121) 1-ethyl-3-[5-[2-[(1R)-1-hydroxyethyl]pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

122) 1-ethyl-3-[5-[2-[(1S)-1-hydroxyethyl]pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

123) 4-[3-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]oxetan-3-yl]oxy-4-oxo-butanoic acid;

124) 4-[2-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-2-hydroxy-propoxy]-4-oxo-butanoic acid;

125) 1-ethyl-3-[5-[2-(4-hydroxytetrahydropyran-4-yl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

126) 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl 2-aminoacetate;

127) 1-ethyl-3-[5-[2-(4-hydroxytetrahydrothiopyran-4-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

128) 1-ethyl-3-[5-[2-(4-hydroxy-1-methyl-4-piperidyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

129) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-(2-aminoethylamino)acetate;

130) 1-[5-[2-[(1R*,2S*)-3,3-difluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (mixture 1-[5-[2-[(1R,2S)-3,3-difluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea; and 1-[5-[2-[(1S,2R)-3,3-difluoro-1,2-dihydroxy-

propyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea);

131) 1-ethyl-3-[7-(2-pyridyl)-5-[2-[(1R*,2S*)-3,3,3-trifluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea (mixture 1-ethyl-3-[7-(2-pyridyl)-5-[2-[(1R,2S)-3,3,3-trifluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea; and 1-ethyl-3-[7-(2-pyridyl)-5-[2-[(1S,2R)-3,3,3-trifluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea);

132) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] (2S)-2-aminopropanoate;

133) 4-[(1S)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethoxy]-4-oxo-butanoic acid;

134) 4-[(1R)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethoxy]-4-oxo-butanoic acid;

135) 1-[5-[2-(1,2-dihydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

136) 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl 2-amino-2-methyl-propanoate;

137) 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl 3-aminopropanoate;

138) tert-butyl 4-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-4-hydroxy-piperidine-1-carboxylate;

139) 1-ethyl-3-[5-[2-(4-hydroxy-1-oxo-thian-4-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

140) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-(dimethylamino)acetate;

141) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-morpholinoacetate;

142) 1-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-5-[2-[(1R)-1-hydroxyethyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

143) 1-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-5-[2-[(1S)-1-hydroxyethyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

144) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 5-aminopentanoate;

145) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 5-(dimethylamino)pentanoate;

146) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-aminoacetate;

147) 1-[7-[4-[(3,3-difluoroazetidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

148) 1-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-5-[2-(3-hydroxyoxetan-3-yl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

149) 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl dihydrogen phosphate;

150) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-methoxyethylamino)-1,3-benzothiazol-2-yl]urea;

151) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-morpholino-1,3-benzothiazol-2-yl]urea;

152) [(1R)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] dihydrogen phosphate;

153) [(1S)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] dihydrogen phosphate;

154) 1-ethyl-3-[5-[2-(3-hydroxyoxetan-3-yl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

155) 1-ethyl-3-[7-[4-[(3-methoxyazetidin-1-yl)methyl]-2-pyridyl]-5-[6-[2,2,2-trifluoro-1-hydroxy-ethyl]-3-pyridyl]-1,3-benzothiazol-2-yl]urea;

156) 1-[7-[4-[(4,4-difluoro-1-piperidyl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

157) 1-[5-[2-[1,2-dihydroxy-1-methyl-ethyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea;

158) 1-ethyl-3-[5-[2-[1-hydroxyethyl]pyrimidin-5-yl]-7-(5-methyl-2-pyridyl)-1,3-benzothiazol-2-yl]urea;

159) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(4-methylpiperazin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

160) [(1S)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] (2S)-pyrrolidine-2-carboxylate;

161) [(1R)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] (2S)-pyrrolidine-2-carboxylate;

162) tert-butyl 3-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-3-hydroxy-azetidine-1-carboxylate;

163) 1-ethyl-3-[5-[2-(3-hydroxyazetidin-3-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

164) 1-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

165) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-[[(2S)-pyrrolidine-2-carbonyl]amino]acetate;

166) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] (2S)-pyrrolidine-2-carboxylate;

167) 4-[3-[5-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-2-(ethylcarbamoylamino)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]oxetan-3-yl]oxy-4-oxo-butanoic acid;

168) 1-ethyl-3-[7-[5-(1-hydroxyethyl)-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

169) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-(2-morpholinoethylamino)acetate;

170) 2-[[2-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethoxy]-2-oxo-ethyl]amino]acetic acid;

171) (2S)-2-amino-4-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethoxy]-4-oxo-butanoic acid;

172) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 4-aminobutanoate;

173) 1-ethyl-3-[5-[2-(4-hydroxy-1,1-dioxo-thian-4-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

174) 1-ethyl-3-[5-[2-(4-hydroxy-4-piperidyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

175) 1-[7-[4-[(3-ethoxyazetidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

176) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-methoxy-1,3-benzothiazol-2-yl]urea;

177) 1-ethyl-3-[6-fluoro-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

178) 1-ethyl-3-[7-(3-fluoro-4-methoxy-2-pyridyl)-5-[2-[1-hydroxyethyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

179) 3-[[2-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethoxy]-2-oxo-ethyl]amino]propanoic acid;

180) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] (3R)-pyrrolidine-3-carboxylate;

181) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] (3R)-morpholine-3-carboxylate;

182) 1-[6-(cyclopropylmethoxy)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

183) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-methoxyethoxy)-1,3-benzothiazol-2-yl]urea;

184) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-(2-phosphonooxyethylamino)acetate;

185) 1-ethyl-3-[5-[2-[1-hydroxyethyl]pyrimidin-5-yl]-7-[4-(thiomorpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

186) 1-ethyl-3-[6-(2-hydroxyethoxy)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

187) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(thiomorpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

188) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(1-oxo-1,4-thiazinan-4-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

189) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-[2-methoxyethyl(methyl)amino]-1,3-benzothiazol-2-yl]urea;

190) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] dihydrogen phosphate;

191) 1-[7-[4-[(1,1-dioxo-1,4-thiazinan-4-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

192) 1-[6-[(3,4-dimethoxyphenyl)methoxy]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

193) 1-ethyl-3-[5-[2-[1-hydroxyethyl]pyrimidin-5-yl]-6-(tetrahydrofuran-2-ylmethoxy)-1,3-benzothiazol-2-yl]urea;

194) 1-ethyl-3-[5-[2-[1-hydroxyethyl]pyrimidin-5-yl]-6-morpholino-1,3-benzothiazol-2-yl]urea;

195) 1-[7-[(3S)-3-aminopyrrolidin-1-yl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

196) 1-ethyl-3-[7-[4-[(2-hydroxyethylamino)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

197) 1-ethyl-3-[5-[5-(1-hydroxyethyl)-3-pyridyl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

198) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

199) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-morpholinoethoxy)-1,3-benzothiazol-2-yl]urea;

200) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-methoxyethylsulfanyl)-1,3-benzothiazol-2-yl]urea;

201) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-methoxyethylsulfinyl)-1,3-benzothiazol-2-yl]urea; and

202) 1-ethyl-3-[5-[2-[(1R)-1-hydroxyethyl]pyrimidin-5-yl]-7-(5-methoxy-2-pyridyl)-1,3-benzothiazol-2-yl]urea.

In a further particular embodiment, esters preferably ester prodrugs of these compounds and their salts, racemates, diastereomers, enantiomers and deuterated forms thereof are preferred. In yet another further particular embodiment, phosphates, preferably phosphate prodrugs of these compounds and their salts, racemates, diastereomers, enantiomers and deuterated forms thereof are preferred. Accordingly, in one embodiment the compound is an ester or phosphate selected from the group consisting of any one of compounds 18, 19, 20, 21, 62, 63, 123, 126, 129, 132, 133, 134, 136, 137, 140, 141, 144, 145, 146, 149, 152, 153, 160, 161, 165, 166, 167, 169, 170, 171, 172, 179, 180, 181, 184 and 190, their salts, racemates, diastereomers, enantiomers and deuterated forms thereof.

The salts of the compound of Formula (I) are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within

the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include, but are not limited to, salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulfuric, phosphoric, nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, malonic, hydroxymaleic, fumaric, malic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluenesulphonic, benzenesulphonic, ethane-1,2-disulfonic, salicylic, sulphanilic, aspartic, glutamic, gentisic, edetic, stearic, palmitic, pamoic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, zinc, ammonium, alkylammonium such as salts formed from triethylamine, alkoxyammonium such as those formed with ethanolamine and salts formed from ethylenediamine, choline or amino acids such as arginine, lysine or histidine. General information on types of pharmaceutically acceptable salts and their formation is known to those skilled in the art and is as described in general texts such as "*Handbook of Pharmaceutical salts*" P. H. Stahl, C. G. Wermuth, 1st edition, 2002, Wiley-VCH.

Basic nitrogen-containing groups may be quarternized with such agents as lower alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others such as alkylphosphonates or phosphoramidates.

Hydroxyl groups may be esterified with groups including lower alkyl carboxylic acids, such as acetic acid and 2,2-dimethylpropionic acid, or sulfonated with groups including alkyl sulfonic acids, such as methyl sulfonic acid or phosphorylated with groups including alkylphosphonic acids, such as methylenephosphonic acid, or directly attached to phosphonate esters, phosphinate esters, or phosphate esters.

It will be recognised that the compounds of formula I may possess asymmetric centres and are therefore capable of existing in more than one stereoisomeric form. The invention thus also relates to compounds in substantially pure isomeric form at one or more asymmetric centres eg., greater than about 90% ee, such as about 95% or 97% ee or greater than 99% ee, as well as mixtures, including racemic mixtures, thereof.

Such isomers may be prepared by asymmetric synthesis, for example using chiral intermediates, or by chiral resolution.

This invention also encompasses prodrugs of compounds of Formula (I). Compounds of Formula (I) having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs.

Particularly preferred are prodrugs of hydroxyl groups such as carbamates, phoshphates, sulfates and ester groups including those derived from amino acids and dipeptides and moieties designed to release the parent via hydrolysis or internal cyclisation of the prodrug moiety.

Compositions

There is also provided a composition comprising a compound of Formula (I) its salts, isomers, racemates, diastereomers, enantiomers and prodrugs thereof.

Preferably, the composition further comprises a pharmaceutically acceptable carrier, diluent or excipient.

The compositions of the present invention may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

Pharmaceutical formulations include those for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The compounds of the invention, together with a conventional adjuvant, carrier or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids as solutions, suspensions, emulsions, elixirs or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use.

In one embodiment the compositions of the present invention are formulated for oral administration and/or intravenous (IV) administration.

In another embodiment the compositions of the present invention may be administered in combination with or additionally comprise another antibacterial agent. Suitable antibacterial agents will be familiar to those in the art and may include

penicillins, cephalosporins, carbapenems, monobactams, beta-lactams, glycopetides, aminoglycosides, tetracyclines, macrolides, ketolides, quinolones, fluoroquinolones, oxazolidinones, coumarins, cyclothialidines, vancomycin and derivatives thereof.

Methods of treatment

The present invention provides a method for the treatment of a bacterial infection comprising administration of a compound of Formula (I) or a pharmaceutically acceptable salt thereof to a subject suffering from said infection.

The compounds of the present invention may be administered by any suitable means, for example, orally, parenterally, such as by subcutaneous, intravenous, intramuscular, or intracisternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions).

The present invention also provides compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of a bacterial infection.

The term "effective amount" means the amount of the subject composition that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired

effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

In the treatment or prevention of bacterial infections, an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

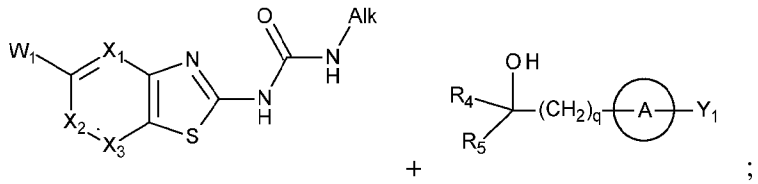
In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, caprine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

The subjects treated in the above method are mammals, including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine,

caprine, equine, canine, feline, rodent or murine species, and preferably a human being, male or female.

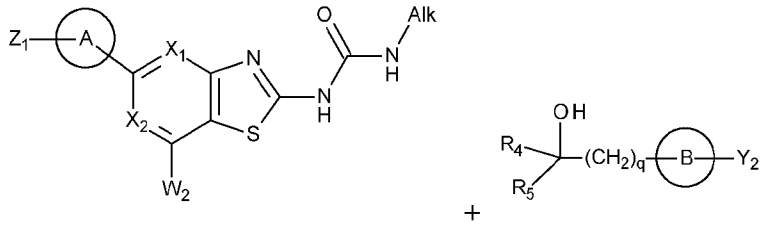
Methods of preparation

Generally, the compounds of the invention may be prepared by coupling an intermediate of formula (i-a) with a precursor of formula (ii-a):



(i-a) (ii-a)

or alternatively coupling an intermediate of formula (i-b) with a precursor of formula (ii-b):



(i-b) (ii-b)

under the conditions described including suitable variations or alternatives thereof in the methods and examples which follow. Formation of compounds of the invention as their salts, racemates, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof is also described.

General Method A

Compounds of the invention may be prepared under Suzuki coupling conditions familiar to those skilled in the art. Suitable conditions include (i) coupling a precursor comprising a boronic acid or a boronate ester thereof with an intermediate comprising a halo (particularly Cl, Br and I) or triflate (or vice versa); (ii) in the presence of a base, such as cesium carbonate or potassium carbonate; (iii) a palladium catalyst, such as $Pd(dppf)Cl_2$ or $Pd(PPh_3)_2Cl_2$; and (iv) an organic solvent, such as dioxane or DMF.

General Method B

Compounds of the invention may be prepared by reduction of a keto moiety to a secondary alcohol under reduction conditions. Suitable conditions include (i) a reducing agent such as $NaBH_4$; and (ii) an organic solvent, such as THF.

General Method C

Compounds of the invention comprising a diol moiety may be prepared by oxidation of an alkene moiety under oxidation conditions. Suitable conditions include (i) an oxidizing reagent such as OsO_4; and (ii) an organic solvent, such as pyridine.

General Method D

Compounds of the invention comprising a diol moiety may be prepared under epoxide ring opening conditions familiar to those in the art.

General Method E

Compounds of the invention may be prepared by alkylation of an aldehyde moiety to a secondary alcohol via organo-metallic addition. Suitable conditions include (i) a Grignard reagent such as halo(alkyl)magnesium; and (ii) an organic solvent, such as Et_2O.

General Method F

Compounds of the invention may be prepared under Stille coupling conditions familiar to those in the art. Suitable conditions include (i) coupling a precursor comprising a halo (particularly Cl, Br and I) with an intermediate comprising a stannylated moiety such as tributyltin (or vice versa); (ii) in the presence of palladium catalyst, such as $Pd(PPh_3)_4$; and (iii) an organic solvent, such as DMF.

General Method G

Compounds of the invention may be prepared under Chan-Lam coupling conditions familiar to those in the art. Suitable conditions include (i) coupling a precursor containing an N-H moiety with an intermediate comprising a boronic acid (or vice versa); (ii) in the presence of a copper reagent such as $Cu(OAc)_2.H_2O$ in an oxygen atmosphere.

General Method H

Compounds of the invention containing prodrug forms of the secondary or tertiary alcohol moieties may be formed under suitable conditions familiar to those in the art. Prodrug forms include carbamates, phosphates and esters including those derived from amino acids and dipeptides and suitable conditions to form them are desribed in the examples which follow.

General Method I

Compounds of the invention may be prepared under Buchwald-Hartwig coupling conditions familiar to those in the art. Suitable conditions include (i) coupling a precursor comprising of a halo with an intermediate comprising of a N-H moiety (or vice versa); (ii) in the presence of a palladium catalyst, such as $Pd_2(dba)_3$; (iii) a

suitable ligand, such as Xantphos; (iv) a suitable base such as Cs_2CO_3; and (v) an organic solvent, such as 1,4-dioxane.

Salt Formation Method(s)

Salts of the compounds of the invention may be formed using conditions familiar to those in the art, for example, as follows.

General salt formation conditions

The free base material is dissolved or suspended in an organic solvent, organic solvent mixture or organic solvent water mixture (for example; DCM, THF, THF/MeOH, EtOH) and a solution/suspension of the acid in the same organic solvent or organic solvent mixture in molar equivalents of 1 or greater than 1 is added. The acid may also be added neat. The salt product may precipitate at room temperature or alternatively the addition may be done at a higher temperature with subsequent cooling to enable precipitation of the salt product. An antisolvent (for example; hexanes, n-heptane, Isopropyl acetate) may be added after the addition of acid to enable precipitation of the salt product which is collected by vacuum filtration and washed with an appropriate organic solvent.

Example hydrochloride salts

Hydrochloride salts can be made, for example, by suspending the compound in a suitable solvent, such as acetonitrile, and adding aqueous 2M hydrochloric acid solution. Dilution of the mixture with water and then removal of the solvent gives the hydrochloride salt of the compound.

Example methanesulphonic acid salts

Methanesulphonic acid salts can be made, for example, by suspending the compound in a suitable solvent, such as acetonitrile, and adding 1 equivalent of methanesulphonic acid in water. Removal of the solvent gives the methanesulphonic acid salt of the compound.

Chiral Separation Method(s) and Synthesis

Compounds of the invention may be separated into their diastereoisomers or enantiomers under chiral HPLC conditions familiar to those in the art. Alternatively, chiral precursor moieties may be resolved from their racemates via derivatization with a chiral auxiliary, such as a blocked amino acid, e,g, Boc-valine, separated by fractional crystallization of diastereomers from a suitable solvent, such as heptane, and reconstitution of the enantiomeric precursors through cleavage of the auxiliary, such as base-mediated cleavage on resin or in solution. Mitsonobu-type inversion of

enantiomerically enriched mixtures of chiral alcohols can also be accomplished by coupling the alcohol with the chiral auxiliary, such as an amino acid, e.g. Boc-valine, in the presence of trialkylated phosphines, such as triphenylphosphine, and dialkylazodicarboxylates, and fractionally crystallizing the enriched diastereomeric mixture as above.

Protecting Groups

During the reactions a number of the moieties may need to be protected. Suitable protecting groups are well known in industry and have been described in many references such as Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. It will be understood that in addition to protecting groups such as hydroxyl and amino groups during the course of reaction, the urea moiety may require protection under any of the reactions conditions described herein, for example, as a 5-methyl-1,3,5-triazinan-2-one.

Functional Group Interconversions

Further, it will be understood that compounds of the invention produced under any of the reaction conditions described herein may undergo further functionalisation under suitable conditions familiar to thoes in the art. That is, the skilled person will appreciate that a wide diversity of compounds may be provided by functional group interconversions of hydroxyls and carboxylates including but not limited to halogens, ethers, ketones, carboxylic acids, esters, carbonates, amines, amides, ureas, carbamates, sulfates, sulfonamides, phosphates, heterocycles, heteroaryls, optionally substituted alkyl chain extensions and so on.

EXAMPLES

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. The invention will now be described without limitation by reference to the examples which follow.

The abbreviations used in the Examples are as follows unless indicated otherwise.

Abbreviations

Ac:	acetyl
ACN:	acetonitrile
cfus:	colony forming units
DCM:	dichloromethane
DIPEA:	*N,N*-diisopropylethylamine

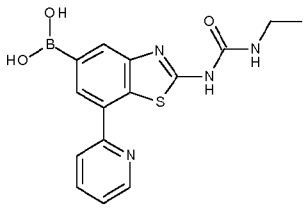
DMAP:	*N,N*-dimethylpyridin-4-amine
DMF:	*N,N*-dimethylformamide
DMSO:	dimethylsulfoxide
EtOAc:	ethyl acetate
Et_2O :	diethyl ether
EtOH :	ethanol
g:	gram(s)
h:	hour(s)
H_2O:	Water
HPLC:	high performance liquid chromatography
IPA:	propan-2-ol
kg:	kilogram(s)
L:	litre(s)
LCMS:	liquid chromatography coupled mass spectrometry
LDA:	lithium diisopropylamide
M:	molar
mg:	milligram(s)
min:	minute(s)
mL:	millilitre(s)
MeOH:	methanol
mol:	mole(s)
mmol:	millimole(s)
MS:	mass spectrometry
NBS:	*N*-bromosuccinimide
NMP:	1-methylpyrrolidin-2-one
NMR:	nuclear magnetic resonance
$Pd(dppf)Cl_2$: adduct	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), DCM
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
RT:	room temperature
THF:	tetrahydrofuran
TLC:	thin-layer chromatography

Compound Synthesis

^{1}H NMR spectra were recorded on either a Brüker Avance DRX 400, AC 200 or AM 300 spectrometer. Spectra were recorded in deuterated solvents ($CDCl_3$, MeOD, DMSO-d_6, CD_3CN, or Acetone-d_6) using the residual solvent peak as a reference. Chemical shifts are reported on the δ scale in parts per million (ppm) using the following conventions to assign the multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and prefixed br (broad). Mass spectra (ESI) were recorded on either a Micromass Platform QMS or Thermo Finnigan LCQ Advantage spectrometer. Flash chromatography was performed on 40-63μm silica gel 60 (Merck No. 9385). Automated flash chromatography was performed either on a Combi-Flash™ purification system using Combi-Flash™ silica gel columns or on a Biotage SP4 purification system using either GraceResolv™ silica gel cartridges, Grace Reveleris™ C-18 reverse phase silica gel cartridges or Biotage SNAP™ C-18 reverse phase silica gel cartridges. Preparative HPLC was carried out using either a Gilson 322 pump with a Gilson 215 liquid handler and a HP1100 PDA detector or an Agilent 1200 Series mass detected preparative LCMS using a Varian XRs C-18 100 x 21.2 mm column. Unless otherwise specified, the HPLC systems employed Phenomenex C8(2) columns using either acetonitrile or acetonitrile containing 0.06 % TFA in water, water containing 0.1 % TFA or water containing 0.1 % formic acid.

Example(s) of Intermediates

[2-(ethylcarbamoyl amino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]boronic acid (**Intermediate 1**)



^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.10 (t, J= 7.20 Hz, 3H), 3.20 (m, 2H), 6.84 (br s, 1H), 7.41 (m, 1H), 8.01 (m, 1H), 8.12 (s, 1H), 8.25 (m, 3H), 8.40 (s, 1H), 8.79 (d, J= 4.0 Hz, 1H) and 10.57 (br s, 1H). MS: 343.25 $[M+H]^+$.

2-amino-3-bromo-5-nitro-phenol (i): To a stirred solution of 2-amino-5-nitro-phenol (500 g, 3.24 mol) in ACN (12 L) was added bromine (290 mL, 5.63 mol) drop wise over a period of 30 min. The mixture was stirred at 30-35°C for 1 h, then the solvent was evaporated to dryness. Hexane (2 L) was added and the mixture evaporated to dryness. Hexane (5 L) was added and the mixture stirred for 1 h and filtered. The solid (1102 g) was washed with hexane (2 L). The residue was added to ice-cold H_2O (2.5 L) followed by the addition of a saturated solution of sodium thiosulfate (2.5 L) and extraction with EtOAc (2 x 10 L). The combined organic layers were washed with

brine, dried (Na_2SO_4), filtered and concentrated at 40-45°C in vacuo to obtain **i** (643 g, 85%).

*3-bromo-5-nitro-phenol (**ii**):* To a cooled solution (-10°C) of **i** (643 g, 2.76 mol) in EtOH (13 L) was added conc. H_2SO_4 (515 mL, 9.97 mol) over a period of 35 min at -10 to -2°C. The mixture was allowed to warm to RT and then heated to 50-55°C followed by the portion-wise addition of $NaNO_2$ (671 g, 9.72 mol) over 30 min and the mixture heated at reflux for 3 h. The mixture was concentrated to 3 L and cooled to 0°C followed by the addition of H_2O (5 L) and extraction with EtOAc (3 x 6 L). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was treated with 25% ether-hexane mixture (6 L) and stirred for 1 h, filtered and the solid and washed with hexane (3 L) to obtain **ii** (505 g, 84%).

*1-benzyloxy-3-bromo-5-nitro-benzene (**iii**):* To a solution of **ii** (770 g, 3.53 mol) in acetone (10 L) was added K_2CO_3 (2.45 kg, 17.75 mol) at RT followed by benzyl bromide (632 mL, 5.32 mol) over a period of 30 min. The mixture was stirred for 15 min and then heated at reflux for 3 h.The mixture was filtered through celite and the acetone was distilled off. The residue was purified over silica eluting with EtOAc: hexane (5:95) to obtain **iii** (551 g, 51%).

*3-benzyloxy-5-bromo-aniline (**iv**):* To a solution of **iii** (551 g, 1.78 mol) in THF (11 L) was added $SnCl_2.2H_2O$ (2.17 kg, 9.62 mol) at RT. The mixture was refluxed for 3h. The mixture was cooled to 0-5°C and basified with saturated $NaHCO_3$ solution and extracted with EtOAc (4 x 5 L). The combined organic layer were washed with brine, dried (Na_2SO_4), filtered and concentration in vacuo gave **iv** (480 g, 97%).

*N-[(3-benzyloxy-5-bromophenyl)carbamothioyl] benzamide (**v**):*To a solution of **iv** (480 g, 1.73 mol) in acetone (10 L) was added benzoylisothiocyanate (280 mL, 2.08 mol) at RT and the mixture stirred for 45 min. The acetone was distilled off and hexane (2 L) added and the mixture concentrated to dryness. To the residue was added hexane (4 L) and the mixture heated to 40°C for 30 min The solid was collected by filtration and washed with hexane (2 x 2 L) to obtain **v** (648 g, 85%).

*(3-benzyloxy-5-bromo-phenyl)thiourea (**vi**):* To a solution of **v** (648 g, 1.47 mol) in THF (12 L) was added NaOH solution (300 g, 7.5 mol in 3 L H_2O) at RT. The mixture was heated at 70°C overnight. The THF layer was decanted off and the aqueous layer was extracted with EtOAc (3 x 2 L). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue

was treated with mixture of Et_2O and hexane (5:95, 3.0 L), filtered, washed with hexane and dried under high vacuum to obtain **vi** (387 g, 78%).

*5-benzyloxy-7-bromo-1,3-benzothiazol-2-amine (**vii**):* To an ice-cold suspension of **vi** (372 g, 1.10 mol) in ACN (6 L) was added dropwise a solution of bromine (65 mL 1.26 mol in 50 mL ACN) over a period of 30 min. The mixture was stirred for 30 min at 0-5°C and then slowly allowed to warm to RT and stirred for 1 h. The solid was filtered off and washed with hexane (2 x 3 L). The solid residue was taken in ice H_2O, basified with aq. NH_3 (pH 10-12) and stirred for 30 min at 5-10°C. The resulting solid was filtered off and washed with H_2O and dried under high vacuum to obtain **vii** (216 g, 59%). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 5.12 (s, 2H), 6.92 (d, J= 2.40 Hz, 1H), 6.98 (d, J= 2.0 Hz, 1H), 7.30-7.45 (m, 5H) and 7.69 (br s, 2H). MS: 334.79 $[M+H]^+$.

*1-(5-benzyloxy-7-bromo-1,3-benzothiazol-2-yl)-3-ethyl-urea (**viii**):* To a suspension of **vii** (216 g, 0.64 mol) in 1,4-dioxane (4 L) was added ethylisocyanate (380 mL, 4.81 mol). The mixture was heated up to 80-85°C overnight. The solvent was distilled off and the residue was co-evaporated with hexane. The residue was treated with H_2O at 78-80°C for 3-5 h. The resulting solid was filtered off and washed with hot H_2O, dried under high vacuum to obtain **viii** (196 g, 75%). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, J= 7.20 Hz, 3H), 3.18 (q, J= 6.80 Hz, 2H), 5.17 (s, 2H), 6.71 (br s, 1H), 7.15 (d, J= 2.0 Hz, 1H), 7.26 (br s,1H), 7.31-7.47 (m, 5H) and 10.82 (br s, 1H). MS: 405.90 $[M+H]^+$.

*1-[5-benzyloxy-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (**ix**):* To a stirred solution of **viii** (110 g, 0.27 mol) in DMF (1.1 L) was added 2-tributylstannyl pyridine (298 g, 0.81 mol). The resulting solution was purged with N_2 for 15-20 min followed by addition of $Pd(PPh_3)_4$ (25.41 g, 0.022 mol). The resulting reaction mixture was heated to 100°C under N_2 atmosphere for 15-16 h. The reaction was cooled to 40-45°C and filtered through celite. The celite was washed with DMF (500 mL) and hot EtOAc (1.50 L) and the combined filtrate concentrated at 60-70°C in vacuo. The residue was purified through silica (20% EtOAc-Hexanes to 100% EtOAc) to obtain **ix** (76 g, 70%). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, J= 7.20 Hz, 3H), 3.19 (q, J= 6.80 Hz, 2H), 5.26 (s, 2H), 6.84 (br s, 1H), 7.32-7.43 (m, 5H), 7.51 (d, J= 7.20 Hz, 2H), 7.69 (d, J= 2.0 Hz, 1H), 7.95 (m, 1H), 8.25 (m, 1H), 8.78 (m, 1H) and 10.46 (br s, 1H). MS: 405.30 $[M+H]^+$.

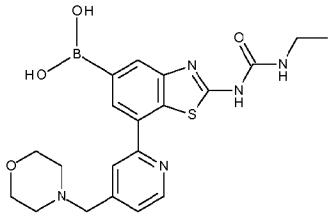
*1-ethyl-3-[5-hydroxy-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea (**x**):* To a stirred solution of **ix** (76 g, 0.187 mol) in DCM (1.7 L) was added methane sulfonic acid (270 mL, 4.17 mol) dropwise over 30 min. The mixture was stirred at RT for 3h. The reaction was concentrated in vacuo. EtOAc (1 L) was added to the residue and this solution was poured carefully onto the crushed ice. The pH of the solution was modified to 8-9 by addition of saturated $NaHCO_3$ solution followed by extraction with EtOAc (3 x 5L). The combined organics were washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was stirred in Et_2O (1.0 L) for 1 h at RT and then filtered to obtain **x** (57.0 g, 97%). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, J= 7.20 Hz, 3H), 3.20 (m, 2H), 6.86 (br s, 1H), 7.0 (s, 1H), 7.46 (s, 2H), 7.96 (m, 1H), 8.10 (m, 1H), 8.76 (m, 1H), 9.59 (br s, 1H) and 10.41 (br s, 1H). MS: 315.06 $[M+H]^+$.

*[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl] trifluoromethanesulfonate (**xi**):* To a stirred solution of **x** (57 g, 0.181 mol) in DMF (1.7 L) was added *N*-phenylbis(trifluromethane sulphonimide) (80.74 g, 0.226 mol) and DIPEA (28 g, 0.217 mol). The mixture was stirred at RT for 3h. The reaction was concentrated at 60-70°C in vacuo. Et_2O was added to the residue and evaporated to dryness. The residue thus obtained was stirred with Et_2O (1.5 L) for 1h and then filtered to obtain **xi** (55.0 g, 68%). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.11 (t, J= 7.20 Hz, 3H), 3.20 (m, 2H), 6.81 (br s, 1H), 7.50 (m, 1H), 7.78 (d, J= 2.0 Hz, 1H), 8.01 (m, 1H), 8.12 (d, J= 2.40 Hz, 1H), 8.35 (m, 1H), 8.84 (m, 1H) and 10.77 (br s, 1H). MS: 446.98 $[M+H]^+$.

*[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]boronic acid (**Intermediate 1**):* To a stirred solution of **xi** (25 g, 56.1 mmol) in DMSO (250 mL) at RT was added bis(neopentylglycolato) diboron (25.2 g, 112 mmol) and KOAc (16.5 g, 168 mmol). The resulting reaction mixture was de-gassed by purging N_2 for 15-20 min followed by addition of $Pd(dppf)Cl_2$ (6.8 g, 8.4 mmol). The mixture was purged with N_2 for 15-20 min and then heated to 80°C for 90 min. The reaction was poured onto saturated NH_4Cl solution (1 L). The resulting precipitate was filtered and dried under vacuum. The solid cake was taken in 2M NaOH (200 mL) and stirred for 45 min at RT. The solution was filtered and the filtrate was acidified upto pH 5-6 and the resulting solid collected by filtration to give **Intermediate 1** (17 g, 88%).

The following intermediate(s) were similarly prepared:

[2-(Ethylcarbamoyl amino)-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-5-yl]boronic acid (**Intermediate 2**)

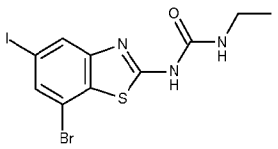


MS: 413.13 $[M+H]^+$.

Prepared in analogous manner to **Intermediate 1** with the exception that the addition of the C7-substituent to 1-(5-benzyloxy-7-bromo-1,3-benzothiazol-2-yl)-3-ethyl-urea was performed under Suzuki coupling conditions instead of Stille coupling conditions as follows:

*1-[5-benzyloxy-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]-3-ethyl-urea (**i**):* A mixture of 1-(5-benzyloxy-7-bromo-1,3-benzothiazol-2-yl)-3-ethyl-urea (27.7 g, 68.3 mmol), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (18.2 g, 80.7 mmol) and potassium acetate (12.2 g, 124 mmol) was suspended in DMSO (120 mL). The mixture was degassed for 15 min with a stream of N_2. $Pd(dppf)Cl_2$ (5.07 g, 6.21 mmol) was added and the mixture heated for 6 h at 85°C, then cooled to RT. A solution of **Precursor 10** (13.2 g, 62.1 mmol) in DMSO (20 mL) was added, followed by Cs_2CO_3 (30.3 g, 93.1 mmol) and H_2O (30 mL). The mixture was degassed for 10 min under a stream of N_2. $Pd(PPh_3)_2Cl_2$ (4.36 g, 6.21 mmol) was added and the mixture heated at 85°C overnight. The solution was cooled and diluted with water (400 mL), stirred vigorously until a solid formed and the supernatant discarded. The solids were suspended in EtOAc/DCM (300 mL) and filtered through a short plug of silica gel, eluting with 5-10% MeOH/DCM. The solution was then concentrated, dissolved in DCM (500 mL) and stirred with 3M HCl (150 mL) for 2 days at RT. The precipitate was collected by filtration, washing with DCM and H_2O. The resulting solid material was suspended in EtOAc/DCM (200 mL), sonicated and the solid collected by filtration to obtain **i** (25.5 g). MS: 504.17 $[M+H]^+$.

1-(7-bromo-5-iodo-1,3-benzothiazol-2-yl)-3-ethyl-urea (**Intermediate 3**)



^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, J= 7.20 Hz, 3H), 3.20 (q, J= 6.80, 2H), 6.73 (br s, 1H), 7.72 (s, 1H), 7.96 (s, 1H) and 11.07 (br s, 1H). MS: 426.0 $[M+H]^+$.

2-bromo-4,6-dinitroaniline (i): To a stirred mixture of H_2O (3.75 L) and acetic acid (375 mL) at RT was added 2,4-dinitroaniline (500 g, 2.73 mol) followed by drop wise addition of bromine (210 mL, 4.09 mol) over 30 min. The reaction mixture was stirred at RT for 15 min and then heated to 100°C for 2 h. The reaction was cooled to RT and poured onto ice-cold H_2O (5-6 L) and basified (pH 8-10) with aqueous ammonia. The solid was filtered, washed with cold H_2O and dried under vacuum. This solid was washed with n-pentane to obtain **i** (600 g, 84%).

1,2-dibromo-3,5-dinitrobenzene (ii): To a stirred solution of **i** (600 g, 2.28 mol) in ACN (5 L) at RT was added tert-butylnitrite (680 mL, 5.7 mol) and cupric bromide (767 g, 3.43 mol). The mixture was heated to 70°C for 1 h under N_2. The reaction was cooled to RT, acidified with 1M HCl solution, H_2O (4 L) added and extracted with EtOAc (3 x 4 L). The combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo to obtain **ii** (723 g, 97%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.48 (d, J= 2.40 Hz, 1H) and 8.68 (d, J= 2.40 Hz, 1H).

(2-bromo-4,6-dinitro-phenyl) thiocyanate (iii): To a stirred solution of **ii** (723 g, 2.22 mol) in MeOH (7.5 L) at RT was added potassium thiocyanate (431 g, 4.44 mol) and the mixture stirred under N_2 for 16 h. The reaction was filtered and washed with MeOH. The filtrate was concentrated in vacuo. The residue was purified over silica (2-6% EtOAc-hexane) to obtain **iii** (549 g, 81%).

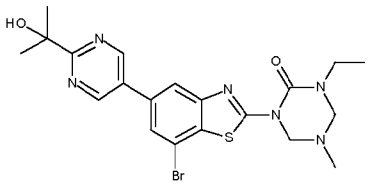
7-bromobenzothiazole-2,5-diamine (iv): To a stirred mixture of EtOH (8.37 L) and H_2O (8.37 L) at RT was added **iii** (549 g, 1.81 mol) followed by addition of Fe powder (2.02 kg, 36.11 mol) and drop wise addition of HCl (12M, 527 mL) over 30 min. The mixture was stirred at RT for 20 min and then heated to 80°C for 45 min. The reaction was cooled to RT, basified to pH 8-10 by addition of aqueous ammonia solution. The solution was passed through celite, washed with EtOAc and the combined filtrate evaporated in vacuo. H_2O (8 L) was added and extracted with EtOAc (2 x 4 L). The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to obtain **iv** (412 g, 93%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.16 (br s, 2H), 6.50 (d, J= 2.0 Hz, 1H), 6.53 (d, J= 1.60 Hz, 1H) and 7.44 (br s, 2H). MS: 243.86 $[M+H]^+$.

7-bromo-5-iodobenzothiazol-2-amine (v): To THF (6 L) at -78°C under N_2 was added BF_3-etherate (50% assay, 708 mL, 2.81 mol) followed by a slow addition of a solution of **iv** (275 g, 1.02 mol) in THF (500 mL) over 20 min. Tert-butyl nitrite (548 L, 4.61

mol) was then added to the solution at -78°C and the mixture was stirred at the same temperature for 40 min and then warmed to -5-0°C. Et_2O was added (at -5-0°C) and the mixture stirred for 20 min. The solid was filtered and taken in acetone at 0°C followed by sequential addition of KI (510 g, 3.07 mol) and iodine (519 g, 2.04 mol) and the mixture stirred at 0°C for 30 min. The reaction was quenched with saturated solution of sodium metabisulfite and extracted with EtOAc (3 x 5 L). The combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo at 45°C. The residue was purified over basic alumina (30-35% EtOAc-hexane) to obtain **v** (235 g, 65%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.50 (d, J= 1.20 Hz, 1H), 7.63 (d, J= 1.20 Hz, 1H) and 7.91 (br s, 2H). MS: 354.90 $[M+H]^+$.

*1-(7-bromo-5-iodobenzothiazol-2-yl)-3-ethylurea (**Intermediate 3**):* To a stirred solution of **vi** (250 g, 0.70 mol) in 1,4-dioxane at RT was added ethylisocyanate (278 mL, 3.52 mol). The mixture was heated to 80°C for 10-12h under N_2. The solvent was evaporated, n-hexane added and the mixture concentrated to dryness. The residue was stirred in hot H_2O (2 L) at 60-65°C for 30-40 min and then filtered. The residue was then treated with a mixture of Et_2O and n-pentane and filtered to obtain **Intermediate 3** (264 g, 88%).

1-[7-Bromo-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-5-methyl-1,3,5-triazinan-2-one (**Intermediate 4**)



^{1}HNMR (DMSO-d_6 400 MHz): δ 9.20 (s, 2H), 8.13 (s, 1H), 7.91 (s, 1H), 5.14 (m, 3H), 4.39 (s, 2H), 3.36 (q, J= 7.20 Hz, 2H), 2.54 (s, 3H), 1.53 (s, 6H) and 1.12 (t, J= 7.20 Hz, 3H).

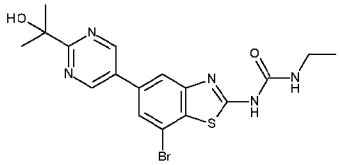
*2-(5-bromopyrimidin-2-yl)propan-2-ol) (**i**):* To an ice-cold solution of methyl 5-bromopyrimidine-2-carboxylate (10 g, 46.1 mmol) in Et_2O (200 mL) was added drop wise methyl magnesium bromide (3.0 M in Et_2O, 61.4 mL, 184 mmol) over 30 min. The reaction mixture was slowly warmed up to RT and continued to stir for 2 h. The mixture was quenched with saturated NH_4Cl solution at 0°C and the organic layer separated from the biphasic solution. The aqueous layer was re-extracted with EtOAc (2 x 250 mL). The combined organic layers were washed with brine solution, dried over Na_2SO_4, filtered and evaporated in vacuo. The crude residue was purified over silica eluting with 20 % EtOAc:hexane to obtain **i** (6.0 g, 62%). 1HNMR (DMSO-d6, 400 MHz): δ 8.97 (s, 2H), 5.15 (s, 1H) and 1.47 (s, 6H).

*2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)propan-2-ol (**ii**):* To the solution of **i** (6.0 g, 27.6 mmol) in 1,4-dioxane (60 mL) was added bis(pinacolato)diboron (8.42 g, 33.2 mmol) and KOAc (4.06 g, 41.5 mmol). The reaction mass was degassed by purging N_2 for 15 min. $Pd_2(dba)_3$ (1.43 g, 1.4 mmol) and tricyclohexylphosphine (0.93 g, 3.31 mmol) was added to the reaction mixture that was degassed for 10 min. The resulting reaction mixture was heated at 80°C for 2 h. The mixture was cooled to RT and filtered through a celite bed. The filtrate was concentrated in vacuo to obtain **ii** (5.11 g, 70%). MS: 265.13 $[M+H]^+$.

*1-(7-bromo-5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)benzo[d]thiazol-2-yl)-3-ethyl-5-methyl-1,3,5-triazinan-2-one (**Intermediate 4**):*To a solution of **Intermediate 3** (7.50 g, 15.48 mmol) and **ii** (5.11 g, 19.36 mmol) in 1,4-dioxane:MeOH (75:50 mL) was added potassium phosphate (6.15 g, 29.03 mmol) at RT. The resulting mixture was degassed for 15-20 min by purging N_2 followed by the addition of $Pd(PPh_3)_4$ (2.23 g, 1.93 mmol). The reaction mixture was again degassed for another 15-20 min and then heated up to 80°C for 2 h. The mixture was cooled to RT and passed through celite bed and washed with EtOAc. The filtrate was evaporated in vacuo and the residue purified over silica eluting with 3%MeOH: DCM to obtain **Intermediate 4** (7.50 g, 97%).

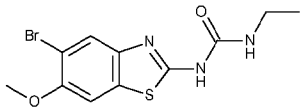
The following intermediate(s) were similarly prepared.

1-[7-bromo-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea (**Intermediate 5**)



MS: 437.91 $[M+H]^+$.

1-(5-Bromo-6-methoxy-1,3-benzothiazol-2-yl)-3-ethyl-urea (**Intermediate 6**)



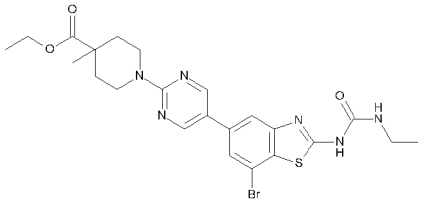
MS: 329.94 & 331.91 $[M+H]^+$.

1-Ethyl-3-(6-methoxy-1,3-benzothiazol-2-yl)urea(i): 6-methoxy-1,3-benzothiazol-2-amine (5.0 g, 27.7 mmol) was dissolved in anhydrous DMSO (20 mL) and triethylamine (15.5 mL, 111 mmol) followed by ethyl isocyanate (4.39 mL, 55.5 mmol) were added. The mixture was stirred at RT under N_2 for 4 h then quenched

with H_2O (~200 mL) and stirred for 1 h. The resulting white solid was collected by filtration and rinsed with H_2O and then with acetone (100 mL) and the filtrate collected separately to the aqueous filtrate. The filtrate was concentrated to dryness in vacuo and combined with the solid collected by filtration to obtain **i** (6.27 g, 90%). MS: 251.96 $[M+H]^+$.

*1-(5-Bromo-6-methoxy-1,3-benzothiazol-2-yl)-3-ethyl-urea (**Intermediate 6**):* Compound **i** (1.10 g, 4.38 mmol) was suspended in DCM (50 mL) and MeOH (5 mL) and bromine (0.34 mL, 6.60 mmol) added. The mixture was stirred at RT for 1.5 h then concentrated to dryness in vacuo to give **Intermediate 6** (2.17 g).

Ethyl 1-[5-[7-bromo-2-(ethylcarbamoylamino)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-4-methyl-piperidine-4-carboxylate (**Intermediate 7**)



^{1}H NMR (DMSO-d_6 400 MHz): δ 1.09 (t, J= 7.20 Hz, 3H), 1.20 (m, 6H), 1.45 (m, 2H), 2.03 (m, 2H), 3.16 (m, 2H), 3.30 (q, J=7.20, 2H), 4.12 (q, J= 6.80 Hz, 2H), 4.25 (m, 2H), 6.75 (br s, 1H), 7.69 (s, 1H), 7.86 (s, 1H); 8.75 (s, 2H) and 10.91 (br s, 1H). MS: 547.11 $[M+H]^+$.

*O1-tert-butyl O4-ethyl 4-methylpiperidine-1,4-dicarboxylate (**i**):* A solution of O1-tert-butyl O4-ethyl piperidine-1,4-dicarboxylate (1.5 g, 5.84 mmol) in THF (25 mL) was cooled to -78°C followed by dropwise addition of LDA (1.80 M in THF, 6.5 mL, 11.68 mmol) at -78°C. The resulting mixture was stirred at -78°C for 45 min followed by addition of methyl iodide (1.2 mL, 17.52 mmol). The temperature was slowly raised up to RT and left at RT for 6 h. The reaction was cooled to 0 °C and quenched by the dropwise addition of saturated NH_4Cl solution (50 mL). The reaction was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by chromatography on silica eluting with 2% EtOAc in hexane gave **i** (1.0 g, 65%).

*Ethyl 4-methylpiperidine-4-carboxylate hydrochloride (**ii**) :* To an ice-cold solution of **i** (1 g, 3.68 mmol) in 1,4-dioxane (10 mL) was added HCl-1,4-dioxane (4.0 M, 15 mL) solution and stirred at RT for 30 min. The solvent was evaporated to obtain **ii** (0.90 g). MS: 172.16 $[M+H]^+$.

*Ethyl 1-(5-bromopyrimidin-2-yl)-4-methylpiperidine-4-carboxylate (**iii**):* To a solution of **ii** (0.9 g, 4.35 mmol) in EtOH (10 mL) was added DIPEA (2.30 mL, 13 mmol) at RT and the mixture stirred at RT for 10 min followed by addition of 5-bromo-2-chloropyrimidine (0.7 g, 3.6 mmol). The mixture was heated at 70 °C for 1h. The

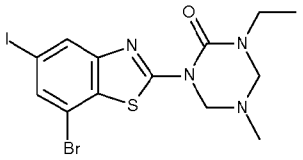
solvent was evaporated and the crude residue purified by chromatography on silica eluting with 1.5% EtOAc: hexane to obtain **iii** (0.90 g, 75%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.17 (s, 3H), 1.21 (t, J= 7.20 Hz, 3H) 1.40 (m, 2H), 2.00 (m, 2H), 3.24 (m, 2H), 4.11 (m, 2H), 4.15 (q, J=7.20 Hz, 2H), 8.43 (s, 2H). MS: 328.08 $[M+H]^+$.

*Ethyl 4-methyl-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)piperidine-4-carboxylate(**iv**):* To the solution of **iii** (25 g, 76.2 mmol) in 1,4-dioxane (250 mL) was added potassium acetate (22.4 g, 228.6 mmol) and bis(pinacolato)diboron (38.7 g, 152.4 mmol). The mixture was degassed for 15-20 min by purging with N_2 followed by the addition of $Pd_2(dba)_3$ (4.0 g, 3.80 mmol) and tricyclohexyl phosphine (2.55 gm, 9.12 mmol). The mixture was again degassed for another 15-20 min and then heated up to 80°C for 3 h. The mixture was cooled to RT and diluted with 500 mL of EtOAc and passed through a celite bed. The filtrate was evaporated to obtain **iv** (20 g, 70%). MS: 376.30 $[M+H]^+$.

*Ethyl 1-(5-(7-bromo-2-(3-ethylureido)benzothiazol-5-yl)pyrimidin-2-yl)-4-methylpiperidine-4-carboxylate (**Intermediate 7**):* To a solution of Intermediate 3 (22.7 g, 53.2 mmol) and iv (20 g, 53.2 mmol) in 1,4-dioxane:MeOH (300:180 mL) was added potassium phosphate (17 g, 79 mmol) at RT. The resulting mixture was degassed for 15-20 min by purging N_2 followed by the addition of $Pd(PPh_3)_4$ (6.1 g, 5.32 mmol). The reaction mixture was again degassed for another 15-20 min and then heated up to 80 °C for 5 h. The reaction mixture was cooled to RT, diluted with EtOAc (500 mL) and passed through celite bed. The filtrate was evaporated and the crude residue was purified by chromatography on silica eluting with 1.5% MeOH: DCM to obtain **Intermediate 7** (12 g, 41%).

<u>1-(7-bromo-5-iodobenzo[d]thiazol-2-yl)-3-ethyl-5-methyl-1,3,5-triazinan-2-one</u>

<u>**(Intermediate 8)**</u>

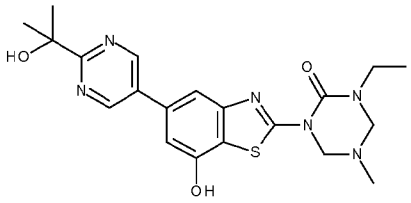


^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.11 (t, *J*= 7.20 Hz, 3H), 2.50 (s, 3H), 3.35 (m, 2H), 4.37 (s, 2H), 5.07 (s, 2H), 7.48 (s, 1H), 8.01 (s, 1H).

To a solution of **Intermediate 3** (50 g, 117.37 mmol) in MeOH (1 L) was added formaldehyde (37% aq solution, 95 mL), methylamine (2M solution in THF, 587 mL, 1.17 mol) and *N*-methylmorpholine (130 mL, 1.17 mmol). The resulting solution was stirred at 75°C for 5-6 h. The MeOH was evaporated in vacuo. Then ice-cold H_2O, was added and the mixture stirred for 30 min and then filtered. The residue was

washed with cold H_2O followed by n-hexane and EtOAc. The residue was dried under high vacuum to give **Intermediate 8** (56 g, quantitative).

1-Ethyl-3-[7-hydroxy-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-5-methyl-1,3,5-triazinan-2-one (**Intermediate 9**)



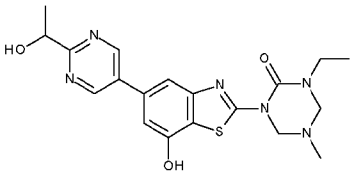
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.83 (s, 2H), 7.34 (s, 1H), 6.82 (s, 1H), 5.07 (s, 2H), 4.63 (s, 1H), 4.21 (s, 2H), 3.37 (q, *J* = 7.0 Hz, 2H), 2.55 (s, 3H), 1.52 (s, 6H), 1.13 - 1.08 (m, 4H). MS: 429 $[M+H]^+$.

*[2-(3-ethyl-5-methyl-2-oxo-1,3,5-triazinan-1-yl)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]boronic acid (**i**):* A mixture of **Intermediate 4** (500 mg), potassium acetate (300 mg), bis(neopentyl glycolato) diboron (460 mg) and $Pd(dppf)_2Cl_2$ (70 mg) in toluene (10mL) was degassed (x3) under vacuum then heated at 130°C for 90 min. The mixture was cooled and filtered through Celite. The filtrate was concentrated to give **i** (465 mg). MS: 457.02 $[M+H]^+$.

*1-ethyl-3-[7-hydroxy-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-5-methyl-1,3,5-triazinan-2-one (**Intermediate 9**):* A solution of Compound ii (465 mg) in acetone (5 mL) was chilled to 0°C then treated dropwise with a solution of oxone (940 mg) in sat $NaHCO_3$ (35 mL). The reaction was stirred at RT overnight, then oxone (100 mg) in sat $NaHCO_3$ (5 mL) was added. The mixture was neutralised with 1M HCl and extracted with 4:1 DCM : IPA (3 x 30 mL). The organic extract was washed with brine (2 0mL) then concentrated. The residue was suspended in 5% MeOH : DCM and purified by chromatography on silica eluting with 0 - 10% MeOH : DCM to give **Intermediate 9** (240mg).

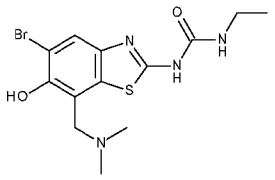
The following intermediate(s) were similarly prepared.

1-ethyl-3-[7-hydroxy-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-5-methyl-1,3,5-triazinan-2-one (**Intermediate 10**)



MS: 415.1 $[M+H]^+$.

1-[5-bromo-7-(dimethylaminomethyl)-6-hydroxy-1,3-benzothiazol-2-yl]-3-ethyl-urea (**Intermediate 11**)

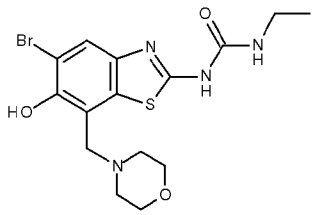


MS 372.89 & 374.87 $[M+H]^+$.

*Preparation of 1-(5-bromo-6-hydroxy-1,3-benzothiazol-2-yl)-3-ethyl-urea (**i**):* **Intermediate 6** (1.30 g, 3.94 mmol) was suspended in hydrogen bromide solution (6.82 mL, 47% aq., 59.1 mmol) and the resulting suspension warmed to 110 °C. Hydrogen bromide solution (14 mL, 47% aq., 121.3 mmol) was added portion-wise over the course of the reaction. After 47 h, the reaction mixture was cooled to RT then in ice and the pH adjusted with sodium hydroxide solution (1 M, aq.) to pH 8. The mixture was filtered and the resulting solid washed with H_2O and ACN. The solid was sucked dry to give **i** (1.01 g, 81%). MS 315.87 & 317.84 $[M+H]^+$.

*1-[5-bromo-7-(dimethylaminomethyl)-6-hydroxy-1,3-benzothiazol-2-yl]-3-ethyl-urea (**Intermediate 11**):* To a mixture of **i** (209 mg, 0.66 mmol) in DMF (2 mL) was added triethylamine (0.14 mL, 0.99 mmol) followed by *N,N*-dimethylmethyleneiminium chloride (147 mg, 0.79 mmol) were added. The mixture was stirred at RT. After 4.25 h, more *N,N*-dimethylmethyleneiminium chloride (~10 mg) was added and stirring continued. After 6 h, the solvent was evaporated with a stream of N_2. The residue was suspended in DCM (~10 mL) and filtered through a PTFE filter. The solid was washed with DCM (~15 ml) and the filtrate concentrated in vacuo to give an oil. The oil was purified by chromatography, on silica eluting with 0-5% MeOH in DCM to give **Intermediate 11** (176 mg, 71%).

1-[5-bromo-6-hydroxy-7-(morpholinomethyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea **(Intermediate 12)**

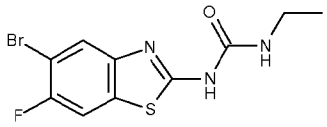


MS 414.93 & 416.91 $[M+H]^+$.

Paraformaldehyde (29 mg, 0.05 mmol) was suspended in anhydrous DMF (2 mL) under argon and morpholine (0.08 mL, 0.95 mmol) added. The mixture was stirred at RT for 10 min then **Intermediate 6** (200 mg, 0.63 mmol) added. The mixture was stirred at RT overnight, heated to 90 °C for 2 h then cooled to RT. The mixture was diluted with H_2O and a precipitate formed. EtOAc was added but the precipitate

remained insoluble. The suspension was filtered through a PTFE filter and the solid rinsed with H_2O and EtOAc. The biphasic filtrate was extracted into EtOAc (4 x 20 mL). The combined organic layers were washed with H_2O (3 x 50 mL), dried (Na_2SO_4) and concentrated in vacuo. The material was purified by chromatography, on silica eluting with 0-10% MeOH in DCM to give **Intermediate 12** (28 mg, 11%).

1-(5-Bromo-6-fluoro-benzothiazol-2-yl)-3-ethyl-urea (**Intermediate 13**)



^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.08 (t, J= 6.80 Hz, 3H), 3.17 (m, 2H), 6.69(br s, 1H), 7.92 (d, J= 6.40 Hz, 1H), 8.0 (d, J= 8.40 Hz, 1H) and 10.86 (br s, 1H).

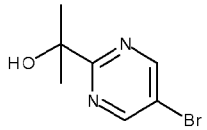
*1-Benzoyl-3-(5-bromo-2,4-difluoro-phenyl)-thiourea (**i**):* To a solution of 5-bromo-2,4-difluoro-aniline (1.0 g, 4.81 mmol) in acetone (25.0 mL) was added drop wise benzoyl isothiocyanate (0.71 mL, 5.29 mmol) and the mixture stirred at RT for 30 min. The solvent was evaporated and the residue washed with hexane and Et_2O to get **i** (1.70 g). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.02-7.06 (m, 1H), 7.56 (t, J=8.0 Hz, 2H), 7.68 (t, J=7.60 Hz, 1H), 7.91 (d, J= 7.60 Hz, 2H), 8.67 (t, J= 7.60 Hz, 1H), 9.15 (br s, 1H) and 12.65 (br s, 1H).

*(5-Bromo-2,4-difluoro-phenyl)-thiourea (**ii**):* To a solution of **i** (1.70g, 4.60 mmol) in THF (35.0 mL) was added a solution of NaOH (0.97 g, 24.25 mmol) in H_2O (13.0 mL). The mixture was stirred at 70°C for 15 h. The THF was evaporated, H_2O added and the mixture extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine and concentrated to obtain **ii** (1.0 g, 83%). MS 267.03 $(M+H)^+$.

*5-Bromo-6-fluoro-benzothiazol-2-ylamine (**iii**):* To a solution of **ii** (0.75 g, 2.80 mmol) in NMP (5.0 mL) was added NaH (0.17 g, 4.21 mmol, 60% dispersion in oil) portion wise. The mixture was heated at 130°C for 2 h. and then poured onto crushed ice and extracted with EtOAc (3 x 50 mL). The combined organics were evaporated. Purification by chromatography on silica eluting with 12% EtOAc-Hexane gave **iii** (0.36 g, 52%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.57 (d, J=6.40 Hz, 1H), 7.66 (br s, 2H) and 7.79 (d, 8.80 Hz, 1H).

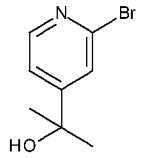
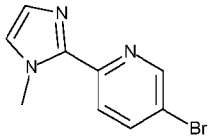
*1-(5-Bromo-6-fluoro-benzothiazol-2-yl)-3-ethyl-urea (**Intermediate 13**) :* To a solution of **iii** (0.36 g, 1.45 mmol) in 1,4-dioxane (25.0 mL) was added ethyl isocyanate (0.69 mL, 8.74 mmol) and the mixture heated at 80°C for 15 h. The solvent was evaporated and the residue stirred with H_2O at 60°C for 5 h. The solution was filtered and washed with Et_2O to obtain **Intermediate 13** (0.30 g, 69%).

Example(s) of Precursor(s)

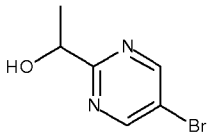
2-(5-Bromopyrimidin-2-yl)propan-2-ol (**Precursor 1**)		^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.8 (s, 2H), 4.3 (s, 1H), 1.6 (s 6H). MS: 218.78 $[M+H]^+$.

Ethyl 5-bromopyrimidine-2-carboxylate (500 mg) was placed in Et_2O (10 mL) and the mixture cooled to 0°C. Methyl magnesium bromide (3M in Et_2O) (1.32 mL) was added dropwise, the reaction allowed to warm to RT and stirred for 30 min. The reaction was quenched by the addition of Na_2CO_3 solution (sat. aq. 2 mL), diluted with H_2O (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography on silica, eluting with a gradient of 0-100% EtOAc in hexane gave **Precursor 1** (256 mg).

The following precursor(s) were similarly prepared.

2-(2-bromo-4-pyridyl)propan-2-ol (**Precursor 2**)	 MS: 216 & 218 $[M+H]^+$.
5-Bromo-2-(1-methylimidazol-2-yl)pyridine (**Precursor 3**)	 MS: 270 $[M+H]^+$.

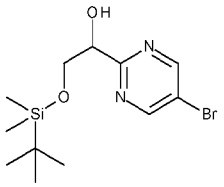
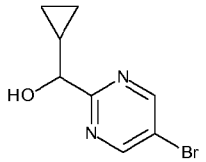
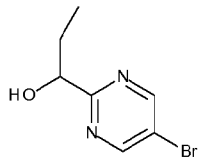
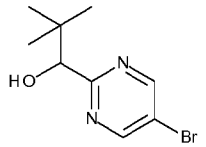
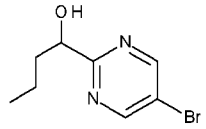
A flask containing 5-bromo-2-iodo-pyridine (500 mg) in THF (2.5 mL) was cooled to -5°C. Isopropyl magnesium chloride (2M in THF) (0.92 mL) was added slowly and the reaction stirred for 50 min. 1-Methylimidazole-2-carbaldehyde (288 mg) was added and the mixture stirred for 3 h. The mixture was cooled to 0°C and 2M HCl added until the pH ~7, then H_2O (2 mL) and toluene (10 mL) were added and the organic layer collected and concentrated. This was partitioned between EtOAc and H_2O and the organic layer dried ($MgSO_4$) and concentrated. The residue was crystallised from EtOAc to give **Precursor 3** (150 mg).

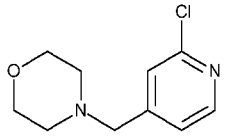
1-(5-Bromopyrimidin-2-yl)ethanol (**Precursor 4**)	

	MS: 204.8 $[M+H]^+$.

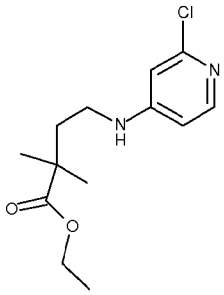
5-Bromo-2-iodo-pyrimidine (1 g) was dissolved in THF (15 mL) and chloro(methyl)magnesium (3M in Et_2O, 2.34 mL) was added at -78°C, then the mixture was stirred at -78°C for 30 min. Acetaldehyde (0.60 mL) was added dropwise to the resulting solution and the reaction was allowed to stir whilst warming to 0°C over 30 min. MeOH was added and the mixture concentrated *in vacuo*. The resultant solid was dissolved in DCM / IPA (5:1; 80 mL) and washed with brine (50 mL). Purification by chromatography on silica, eluting with 0-20% EtOAc in heptane gave **Precursor 4** (244 mg).

The following precursor(s) were similarly prepared.

1-(5-bromopyrimidin-2-yl)-2-[tert-butyl(dimethyl)silyl]oxy-ethanol **(Precursor 5)**	 MS: 332.9 & 334.9, 1:1 $[M+H]^+$.
(5-bromopyrimidin-2-yl)-cyclopropyl-methanol **(Precursor 6)**	 MS: 228.8 $[M+H]^+$.
1-(5-bromopyrimidin-2-yl)propan-1-ol **(Precursor 7)**	 MS: 216.9 $[M+H]^+$.
1-(5-bromopyrimidin-2-yl) -2,2-dimethyl-propan-1-ol **(Precursor 8)**	 MS: 244.9 $[M+H]^+$.
1-(5-bromopyrimidin-2-yl)butan-1-ol **(Precursor 9)**	 MS: 230.9 $[M+H]^+$.

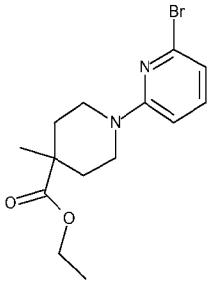
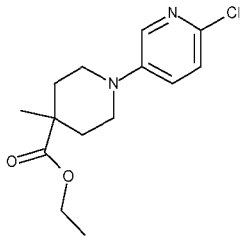
2-Chloro-4-morpholinomethylpyridine (**Precursor 10**)	

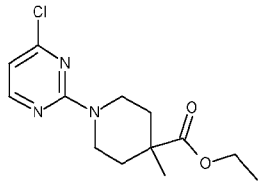
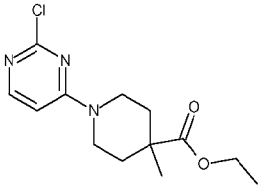
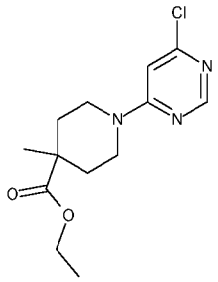
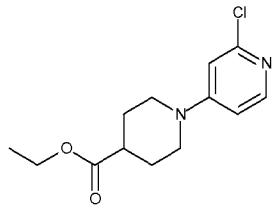
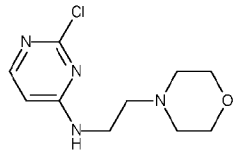
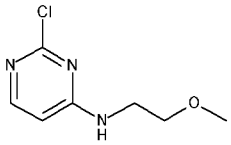
To a solution of 2-chloro-4-(chloromethyl)pyridine (10 g) in THF (200 mL) was added morpholine (5.94 mL) and K_2CO_3 (18.8 g). The mixture was stirred at RT for 3 days. The reaction was filtered, the solids washed with EtOAc, and the filtrate concentrated. This material was purified on a plug of silica (0-50% EtOAc/DCM) to give **Precursor 10** (6.87 g).

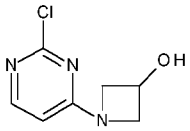
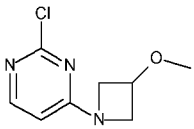
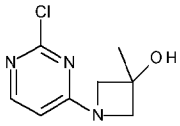
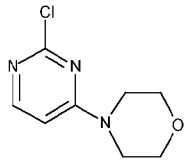
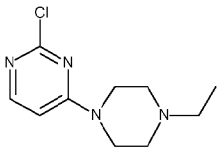
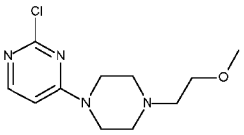
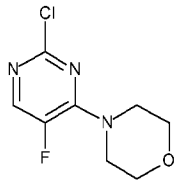
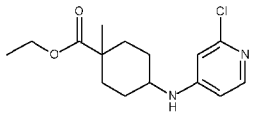
Ethyl 1-(2-chloro-4-pyridyl)-4-methyl-piperidine-4-carboxylate (**Precursor 11**)		^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, *J*= 5.60 Hz, 1H), 6.81-6.83 (m, 2H), 4.10 (q, *J*= 6.80 Hz, 2H), 3.64-3.70 (m, 2H), 3.01-3.08 (m, 2H), 1.97-2.01 (m, 2H), 1.39-1.46 (m, 2H) and 1.16-1.23 (m, 6H).

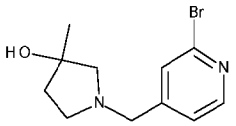
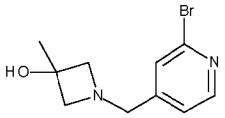
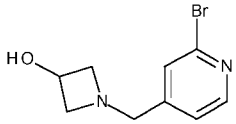
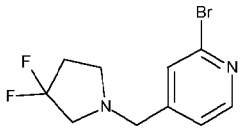
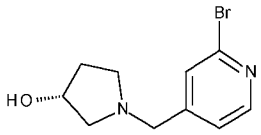
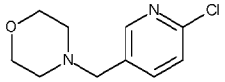
To a solution of 4-bromo-2-chloro-pyridine (2.0 g, 10.39 mmol) in EtOH (25 mL) was added DIPEA (5.50 mL, 31.17 mmol) followed by ethyl 4-methylpiperidine-4-carboxylate hydrochloride (2.60 g, 12.50 mmol). The resulting reaction mixture was heated up to 85°C for 16h. The solvent was evaporated and the residue purified over silica eluting with 20% EtOAc-hexanes to give **Precursor 11** (1.80 g, 75%).

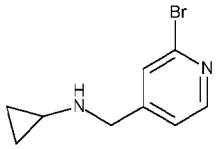
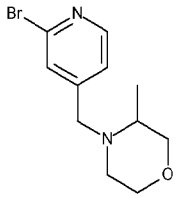
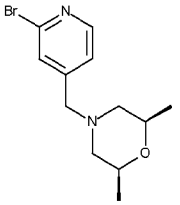
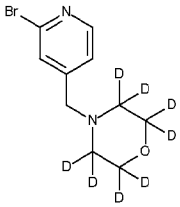
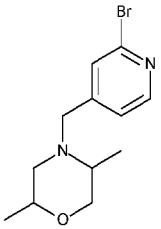
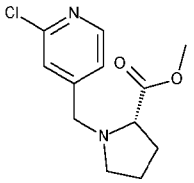
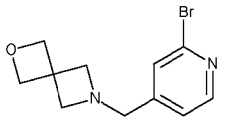
The following precursor(s) were similarly prepared.

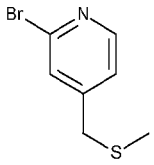
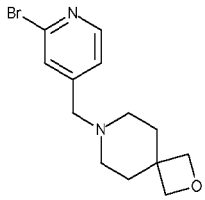
ethyl 1-(6-bromo-2-pyridyl)-4-methyl-piperidine-4-carboxylate (**Precursor 12**)		MS: 327.0 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 1H), 6.70 (d, *J*= 7.60 Hz, 1H), 6.51 (d, *J*= 8.40 Hz, 1H), 4.16 (q, *J*= 6.80 Hz, 2H), 3.88-3.94 (m, 2H), 3.07-3.14 (m, 2H), 2.15-2.18 (m, 2H), 1.43-1.50 (m, 2H) and 1.22-1.28 (m, 6H).
ethyl 1-(6-chloro-3-pyridyl)-4-methyl-piperidine-4-carboxylate (**Precursor 13**)		MS 283.11 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (d, *J*= 2.40 Hz, 1H), 7.63 (dd, *J*= 2.40 and 9.20 Hz, 1H), 6.81 (d, J= 9.20 Hz, 1H), 4.10 (q, *J*= 7.20 Hz, 2H), 3.84-3.89 (m, 2H), 3.05-3.12 (m, 2H), 1.96-2.0 (m, 2H), 1.36-1.43 (m, 2H) and 1.16-1.20 (m, 6H).

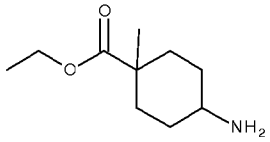
ethyl 1-(4-chloropyrimidin-2-yl)-4-methyl-piperidine-4-carboxylate **(Precursor 14)**		MS 284.19 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.0 (d, *J*= 6.40 Hz, 1H), 6.37 (d, *J*= 6.40 Hz, 1H), 4.20 (q, *J*= 6.80 Hz, 2H), 4.11 (m, 2H), 3.13-3.20 (m, 2H), 2.19-2.22 (m, 2H), 1.40-1.48 (m, 2H) and 1.24-1.29 (m, 6H).
ethyl 1-(2-chloropyrimidin-4-yl)-4-methyl-piperidine-4-carboxylate **(Precursor 15)**		MS 284.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, *J*= 6.0 Hz, 1H), 6.85 (d, *J*= 5.60 Hz, 1H), 4.13 (q, *J*= 7.20 Hz, 2H), 3.99 (m, 2H), 3.15-3.21 (m, 2H), 1.98-2.02 (m, 2H), 1.38-1.45 (m, 2H) and 1.17-1.22 (m, 6H).
ethyl 1-(6-chloropyrimidin-4-yl)-4-methyl-piperidine-4-carboxylate **(Precursor 16)**		MS 284.09 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 6.96 (s, 1H), 4.13 (m, 2H), 4.05 (m, 2H), 3.15-3.22 (m, 2H), 1.97-2.01 (m, 2H), 1.37-1.47 (m, 2H) and 1.15-1.21 (m, 6H).
ethyl 1-(2-chloro-4-pyridyl)piperidine-4-carboxylate **(Precursor 17)**		MS $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, *J*= 5.60 Hz, 1H), 6.82-6.84 (m, 2H), 4.07 (q, *J*= 7.20 Hz, 2H), 3.85-3.89 (m, 2H), 2.96-3.02 (m, 2H), 2.60-2.66 (m, 1H), 1.84-1.87 (m, 2H), 1.48-1.57 (m, 2H) and 1.17 (t, *J*= 7.20 Hz, 3H).
2-chloro-N-(2-morpholinoethyl)pyrimidin-4-amine **(Precursor 18)**		MS 243.11 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 7.87(m, 2H), 6.48 (d, *J*= 5.60 Hz, 1H), 3.57 (m, 4H), 3.39 (m, 2H), 2.45 (m, 6H),
2-chloro-N-(2-methoxyethyl)pyrimidin-4-amine **(Precursor 19)**		MS 188.01 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J*= 5.60 Hz, 1H), 6.26 (d, *J*= 5.60 Hz, 1H), 5.47 (br s, 1H), 3.55 (br s, 4H) and 3.37 (s, 3H).

1-(2-chloropyrimidin-4-yl)azetidin-3-ol **(Precursor 20)**		MS 185.98 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, *J*= 6.0 Hz, 1H), 6.37 (d, *J*= 6.0 Hz, 1H), 5.86 (m, 1H), 4.60 (m, 1H), 4.27 (m, 2H) and 3.79 (m, 2H).
2-chloro-4-(3-methoxyazetidin-1-yl)pyrimidine **(Precursor 21)**		MS 200.04 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, *J*= 4.80 Hz, 1H), 6.08 (d, *J*= 6.0 Hz, 1H), 4.28-4.36 (m, 3H), 4.0 (m, 2H) and 3.33 (s, 3H).
1-(2-chloropyrimidin-4-yl)-3-methyl-azetidin-3-ol **(Precursor 22)**		MS 200.06 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, *J*= 5.20 Hz, 1H), 6.05 (d, *J*= 5.60 Hz, 1H), 4.04 (br s, 4H) and 1.61 (s, 3H).
4-(2-chloropyrimidin-4-yl)morpholine **(Precursor 23)**		MS 200.06 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, *J*= 6.0 Hz, 1H), 6.39 (d, *J*= 6.0 Hz, 1H), 3.78 (m, 4H) and 3.64 (m, 4H).
2-chloro-4-(4-ethylpiperazin-1-yl)pyrimidine **(Precursor 24)**		^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, *J*= 6.0 Hz, 1H), 6.38 (d, *J*= 5.60 Hz, 1H), 3.67 (m, 4H), 2.52 (m, 4H), 2.48 (q, *J*= 7.20 Hz, 2H) and 1.12 (t, *J*= 7.20 Hz, 3H).
2-chloro-4-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine **(Precursor 25)**		^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, *J*= 6.40 Hz, 1H), 6.38 (d, *J*= 6.0 Hz, 1H), 3.7 (m, 4H), 3.60 (t, *J*= 5.20 Hz, 2H), 3.29 (s, 3H), 2.64 (t, *J*= 5.20 Hz, 2H) and 2.60 (m, 4H).
4-(2-chloro-5-fluoro-pyrimidin-4-yl)morpholine **(Precursor 26)**		MS 218.0 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, J= 6.0 Hz, 1H) and 3.74-3.81 (m, 8H).
ethyl 4-[(2-chloro-4-pyridyl)amino]-1-methyl-cyclohexanecarboxylate **(Precursor 27)**		MS 297.07 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.76 (d, *J*= 5.60 Hz, 1H), 6.75 (d, *J*= 8.0 Hz, 1H), 6.45 (m, 2H), 4.11 (q, *J*= 7.20 Hz, 2H), 2.50 (m, 1H), 2.06-2.08 (m,

		2H), 1.78-1.81 (m, 2H), 1.29-1.36 (m, 4H), 1.21 (t, *J*= 7.20 Hz, 3H) and 1.19 (s, 3H).
1-[(2-bromo-4-pyridyl)methyl]-3-methyl-pyrrolidin-3-ol **(Precursor 28)**		MS 271.97 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29-8.31 (d, *J*= 4.80 Hz, 1H), 7.57 (s, 1H), 7.37-7.38 (d, *J*= 4.40 Hz, 1H), 4.58 (s, 1H), 3.64 (s, 2H), 2.64-2.68 (m, 2H), 2.42-2.44 (m, 2H), 1.72-1.75 (m, 2H) and 1.23 (s, 3H).
1-[(2-bromo-4-pyridyl)methyl]-3-methyl-azetidin-3-ol **(Precursor 29)**		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (d, J= 5.20 Hz, 1H), 7.50 (s, 1H), 7.32 (d, *J*= 4.8 Hz, 1H), 5.21 (s, 1H), 3.61 (s, 2H), 3.33 (s, 2H), 2.90 (d, J= 6.40 Hz, 2H) and 1.36 (s, 3H).
1-[(2-bromo-4-pyridyl)methyl]azetidin-3-ol **(Precursor 30)**		MS 243.07 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (d, *J*= 4.80 Hz, 1H), 7.50 (s, 1H), 7.31 (d, *J*= 5.20 Hz, 1H), 5.35 (d, 1H), 4.17-4.25 (m, 1H), 3.59 (s, 2H), 3.48-3.54 (m, 2H) and 2.77-2.81 (t, *J*= 6.80 Hz, 2H).
2-bromo-4-[(3,3-difluoropyrrolidin-1-yl)methyl]pyridine **(Precursor 31)**		MS 277.07 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (d, *J*= 5.20 Hz, 1H), 7.57 (s, 1H), 7.39 (d, *J*= 5.20 Hz, 1H), 3.67 (s, 2H), 2.90 (m, 2H), 2.72 (m, 2H) and 2.27 (m, 2H).
(3R)-1-[(2-bromo-4-pyridyl)methyl]pyrrolidin-3-ol **(Precursor 32)**		MS 257.05 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (d, J= 5.20 Hz, 1H), 7.56 (s, 1H), 7.37 (d, J= 4.80 Hz, 1H), 5.75 (s, 1H), 4.72 (d, J= 4.40 Hz, 1H), 3.55-3.65 (m, 2H), 2.61-2.68 (m, 2H), and 2.38-2.50 (m, 1H), 2.31-2.38 (m, 1H), 1.95-2.04 (m, 1H) and 1.52-1.59 (m, 1H).
4-[(6-chloro-3-pyridyl)methyl] morpholine		MS 213.04 $[M+H]^+$.

(Precursor 33)		
N-[(2-bromo-4-pyridyl)methyl]cyclopropanamine **(Precursor 34)**		MS 227.05 $[M+H]^+$.
4-[(2-bromo-4-pyridyl)methyl]-3-methyl-morpholine **(Precursor 35)**		MS 271.10 $[M+H]^+$.
(2R,6S)-4-[(2-bromo-4-pyridyl)methyl]-2,6-dimethyl-morpholine **(Precursor 36)**		MS 285.07 $[M+H]^+$.
4-[(2-bromo-4-pyridyl)methyl]-2,2,3,3,5,5,6,6-octadeuterio-morpholine **(Precursor 37)**		MS 265.17 $[M+H]^+$.
4-[(2-bromo-4-pyridyl)methyl]-2,5-dimethyl-morpholine **(Precursor 38)**		MS 285.12 $[M+H]^+$.
methyl (2S)-1-[(2-chloro-4-pyridyl)methyl] pyrrolidine-2-carboxylate **(Precursor 39)**		MS 255.06 $[M+H]^+$.
2-[(2-bromo-4-pyridyl)methyl]-6-oxa-2-azaspiro[3.3]heptane **(Precursor 40)**		MS 269.07 $[M+H]^+$.

2-bromo-4-(methylsulfanylmethyl) pyridine **(Precursor 41)**		MS 220.0 $[M+H]^+$.
7-[(2-bromo-4-pyridyl)methyl]-2-oxa-7-azaspiro[3.5]nonane **(Precursor 42)**		MS 297.16 $[M+H]^+$.

Ethyl 4-amino-1-methylcyclohexanecarboxylate (**Precursor 43**)	 MS 186.20 $[M+H]^+$.

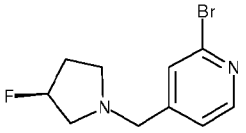
*Ethyl 4-aminocyclohexanecarboxylate (**i**):* To an ice-cold solution of 4-aminocyclohexanecarboxylic acid (5.0 g, 34.92 mmol) in EtOH (20 mL) was added thionyl chloride (7.60 mL, 104.76 mmol).The mixture was heated at 80°C for 3 h. The solvent was evaporated in vacuo to obtain **i** (7.23 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.19 (q, *J*=7.20 Hz, 2H), 3.71 (m, 1H), 2.71 (m, 1H), 2.06 (m, 2H), 1.90 (m, 2H), 1.69 (m, 2H), 1.55 (m, 2H), and 1.25 (t, *J*=7.20 Hz, 3H).

*Ethyl 4-(1, 3-dioxoisoindolin-2-yl) cyclohexanecarboxylate) (**ii**):* A solution of **i** (0.50 g, 2.92 mmol) in toluene (10 mL) was added Et_3N (1.02 mL, 7.30 mmol) and phthalic anhydride (0.56 g, 3.80 mmol). The mixture was refluxed for 8 h using a dean-stark apparatus for removal of H_2O. The solvent was evaporated in vacuo, H_2O (50 mL) added and the mixture stirred for 30 min at RT. The solid material thus obtained was collected by filtration and dried to obtain **ii** (0.30 g, 34%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (s, 4H), 4.19 (q, *J*= 7.20 Hz, 2H), 3.71 (m, 1H), 2.71 (m, 1H), 2.06 (m, 2H), 1.90 (m, 2H), 1.69 (m, 2H), 1.60 (m, 2H), and 1.23 (t, *J*= 7.20 Hz, 3H).

*Ethyl 4-(1,3-dioxoisoindolin-2-yl)-1-methylcyclohexanecarboxylate (**iii**):* A solution of **ii** (0.30 g, 1.0 mmol) in THF (10 mL) was cooled to -78°C followed by dropwise addition of LDA (1.60 M in THF, 1.88 mL, 3.0 mmol) at -78°C. The mixture was stirred at -78°C for 30 min followed by addition of methyl iodide (0.311 mL, 5.0 mmol) at -78°C. The temperature of the reaction mass was slowly raised up to RT and left to stir overnight. The reaction was cooled to 0°C and quenched by dropwise

addition of saturated NH_4Cl solution (30 mL). The reaction was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to obtain **iii** (0.30 g, 97%). MS 316.12 $[M+H]^+$.

*Ethyl 4-amino-1-methylcyclohexanecarboxylate (**Precursor 43**):* To an ice-cold solution of **iii** (0.30 g, 0.95 mmol) in EtOH (20 mL) was added hydrazine hydrate (0.115 mL, 2.38 mmol) and the resulting reaction mixture was heated at 80°C for 3 h. The solvent was evaporated in vacuo, H_2O (20 mL) added and extracted with EtOAc (3 x 50 mL). The organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to give **Precursor 43** (0.18 g).

(S)-2-bromo-4-((3-fluoropyrrolidin-1-yl)methyl)pyridine (**Precursor 44**)		^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.29 (d, *J*= 4.8 Hz, 1H), 7.50 (s, 1H), 7.24-7.26 (d, *J*= 4.8, 1H), 5.12-5.25 (m, 1H), 3.65 (s, 2H) and 2.70-2.91 (m, 3H), 2.45-2.51 (m, 1H), and 2.03-2.25 (m, 2H).MS 259.05 $[M+H]^+$.

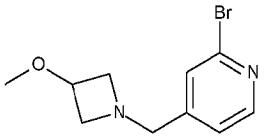
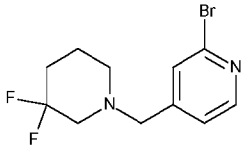
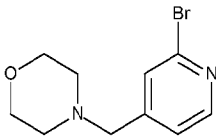
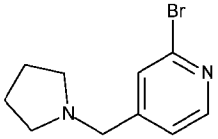
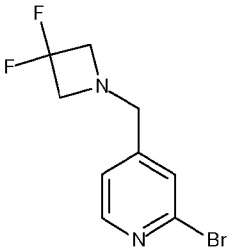
*(2-Bromopyridin-4-yl)methanol (**i**):* To a solution of 2-bromopyridine-4-carbaldehyde (20 g, 107.52 mmol) in MeOH (150 mL) was added portion wise sodium borohydride (12.0 g, 322.56 mmol) at 0°C under inert atmosphere. The mixture was stirred at RT for 1 h. Saturated NH_4Cl solution was added followed by extraction with EtOAc (3 x 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to obtain **i** (18.0 g, 90%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.30 (d, *J*=4.8 Hz, 1H), 7.54 (s, 1H), 7.35 (d, *J*=4.8 Hz, 1H), 5.55 (t, *J*= 6.0 Hz, 1H) and 4.53- 4.54 (d, J=5.6 Hz, 2H).

*2-Bromo-4-(bromomethyl)pyridine) (**ii**):* To the solution of **i** (18 g, 95.74 mmol) in toluene (180 mL) was added dropwise phosphorous tribromide (13.4 mL, 143.62 mmol) at 0°C under inert atmosphere. The mixture was heated at 100°C for 30 min. The reaction was cooled at 0°C and $NaHCO_3$ solution added followed by extraction with EtOAc (2 x 500 mL). The combined organic layer were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified over silica eluting with 15% EtOAc: Hexane to obtain **ii** (12.0 g, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, *J*=4.8 Hz, 1H), 7.51 (s,1H), 7.26 (d, *J*=6.0 Hz, 1H) and 4.34 (s, 2H). MS 251.80 $[M+H]^+$.

*(S)-2-Bromo-4-((3-fluoropyrrolidin-1-yl)methyl)pyridine (**Precursor 44**):* To an ice-cold solution of **ii** (3.0 g, 11.95 mmol) in DMSO (10 mL) was added KOH (1.0 g, 17.92 mmol) followed by the addition of (S)-3-fluoropyrrolidine hydrochloride (2.2 g, 17.92 mmol) under inert atmosphere. The mixture was stirred at 0°C to RT for 20

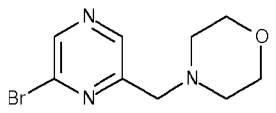
min. The mixture was diluted with ice cold H_2O followed by extraction with EtOAc (3 x 150 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated in vacuo to give **Precursor 44** (3.0 g, 96%).

The following precursor(s) were similarly prepared.

2-bromo-4-[(3-methoxyazetidin-1-yl)methyl]pyridine **(Precursor 45)**		MS 257.19 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.29 (d, *J*= 4.8 Hz, 1H), 7.50 (s, 1H), 7.32 (d, *J*= 4.8 Hz, 1H), 3.95-4.01 (m, 1H), 3.61 (s, 2H), 3.49-3.52 (m, 2H), 3.14 (s, 3H), and 2.86-2.90 (m, 2H).
2-bromo-4-[(3,3-difluoro-1-piperidyl)methyl] pyridine **(Precursor 46)**		MS 291.02 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.34 (d, *J*= 4.80 Hz, 1H), 7.56 (s, 1H), 7.38 (d, *J*= 4.80 Hz, 1H), 3.62 (s, 2H), 2.65 (m, 2H), 2.40 (m, 2H), 1.84-1.90 (m, 2H) and 1.63-1.67 (m, 2H).
4-[(2-bromo-4-pyridyl)methyl] morpholine **(Precursor 47)**		MS 257.49 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.26 (d, *J*= 5.2 Hz, 1H), 7.48 (s, 1H), 7.22 (d, *J*= 4.80 Hz, 1H), 3.69-3.71 (t, *J*= 4.80 Hz, 4H), 3.45 (s, 2H) and 2.41-2.43 (t, *J*= 4.40 Hz, 4H).
2-bromo-4-(pyrrolidin-1-ylmethyl)pyridine **(Precursor 48)**		^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.30 (d, *J*= 4.80 Hz, 1H), 7.55 (s, 1H), 7.37 (d, *J*= 4.80 Hz, 1H), 3.61 (s, 2H), 2.44 (m, 4H) and 1.70 (m, 4H).
2-bromo-4-[(3,3-difluoroazetidin-1-yl)methyl]pyridine (**Precursor 49**)		^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (d, *J*= 4.80 Hz, 1H), 7.47 (s, 1H), 7.25 (d, *J*= 4.80 Hz, 1H), 3.52 (s, 2H) and 3.66 (m, 4H).

To an ice-cold solution of 2-bromoisonicotinaldehyde (0.40 g, 2.15 mmol) in THF (5 mL) was added 3,3-difluoroazetidine hydrochloride (0.41 g, 3.12 mmol) and *N*-methyl morpholine (catalytic). The reaction was stirred at 0°C for 15 min followed by the portion wise addition of sodium cyano borohydride (0.41 g, 6.45 mmol). The mixture was stirred at RT for 16 h. H_2O (50 mL) was added followed by extraction with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried

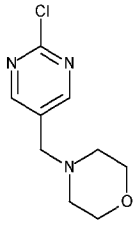
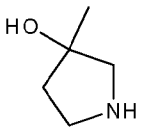
(Na_2SO_4), filtered and concentrated in vacuo. Purification by chromatography on silica (30% EtOAc-Hexane) gave **Precursor 49** (0.18 g, 32%).

4-((6-bromopyrazin-2-yl)methyl)morpholine (**Precursor 50**)		^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.76 (s, 1H), 8.70 (s, 1H), 3.64 (s, 2H), 3.58 (br s, 4H) and 2.43 (br s, 4H). MS 258.0 $[M+H]^+$.

*2-bromo-6-(bromomethyl)pyrazine (**i**):* To a solution of 2-bromo-6-methyl-pyrazine (3.0 g, 17.31 mmol) in CCl_4 (25 mL) was added NBS (4.60 g, 26.01 mmol) and AIBN (0.248 g, 1.734 mmol) at RT. The mixture was stirred at 55°C for 48 h. H_2O was added followed by extraction with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified over silica eluting with 5%EtOAc: Hexane to obtain **i** (1.40 g, 32%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.64 (s, 1H), 8.62 (s, 1H) and 4.50 (s, 2H).

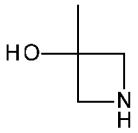
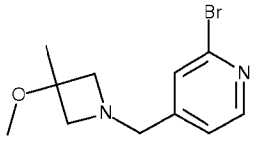
*4-((6-bromopyrazin-2-yl)methyl)morpholine (**Precursor 50**):* To an ice-cold solution of **i** (1.29 g, 4.81 mmol) in ACN (30 mL) was added morpholine (0.46 g, 5.28 mmol) and the mixture stirred at 0°C for 45 min. H_2O was added and the mixture extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified over silica eluting with 90%EtOAc:Hexane to obtain **Precursor 50** (0.6 g, 50%).

The following precursor(s) were similarly prepared.

4-[(2-chloropyrimidin-5-yl)methyl] morpholine (**Precursor 51**)		MS 214.10 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.61 (s, 2H), 3.72 (br s, 4H), 3.52 (s, 2H) and 2.48 (br s, 4H). MS $[M+H]^+$.
3-Methylpyrrolidin-3-ol hydrochloride (**Precursor 52**)		^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.71 (s, 1H), 3.33-3.46 (m, 2H), 1.72-1.74 (m, 2H) and 1.41 (s, 2H), 1.38 (s, 9H) and 1.28 (s, 3H). MS 202.28 $[M+H]^+$.

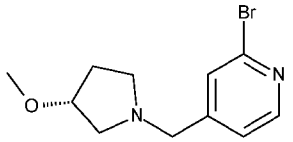
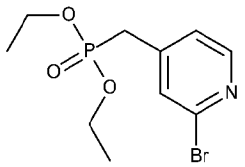
*tert-Butyl 3-hydroxy-3-methylpyrrolidine-1-carboxylate (**i**):* To an ice-cold solution of tert-butyl 3-oxopyrrolidine-1-carboxylate (1.0 g, 5.40 mmol) in Et_2O (20 mL) was added methylmagnesium bromide (3.50 mL, 10.80 mmoL) drop wise under an inert atmosphere. The mixture was stirred at RT for 1 h, then quenched with NH_4Cl

solution followed by extraction with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Trituration with n-pentane gave **i** (1.0 g, 92%).*3-Methylpyrrolidin-3-ol hydrochloride (**Precursor 52**):* To a solution of 4M HCl in 1,4-dioxane (10 mL) at 0°C was added **i** (0.850 g, 4.22 mmol) and the mixture stirred for 2 h at RT. The solvent was removed in vacuo and trituration with Et_2O gave **Precursor 52** (0.490 g). MS 102.15 $[M+H]^+$. The following precursor(s) were similarly prepared.

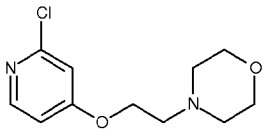
3-methylazetidin-3-ol hydrochloride **(Precursor 53)**		^{1}H NMR (400 MHz, DMSO-d_6): δ 3.81-3.83 (m, 2H), 3.69-3.72 (m, 3H), 2.83 (br s, 1H) and 1.42 (s, 3H).
2-bromo-4-((3-methoxy-3-methylazetidin-1-yl)methyl)pyridine (**Precursor 54**)		MS 271.05 $[M+H]^+$.

To an ice-cold solution of Precursor 29 (0.75 g, 2.92 mmol) in DMF (15 mL) was added NaH (60% dispersion in mineral oil, 0.175 g, 4.38 mmol) portion wise. The mixture was stirred at 0°C for 10 min followed by drop wise addition of methyl iodide (0.27 mL, 4.38 mmol). The reaction mixture was left to stir at 0°C for 30 min. H_2O (10 mL) was added, followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with H_2O, brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified over silica eluting with 40% EtOAc:Hexane to obtain **Precursor 54** (0.24 g, 30%).

The following precursor(s) were similarly prepared.

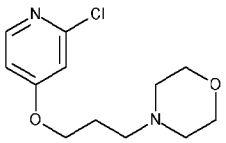
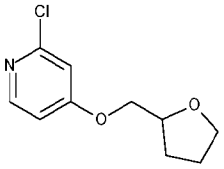
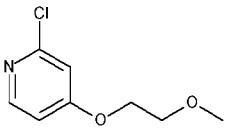
2-bromo-4-[[(3R)-3-methoxypyrrolidin-1-yl]methyl]pyridine (**Precursor 55**)	 MS 271.0 $[M+H]^+$.
2-bromo-4-(diethoxyphosphorylmethyl)pyridine (**Precursor 56**)	 MS 309.98 $[M+H]^+$.

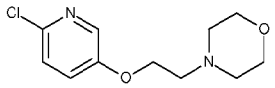
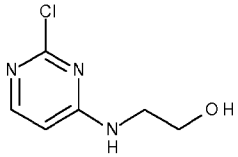
2-bromo-4-(bromomethyl)pyridine (2.3912 mmol; 600 mg and triethylphosphite (2.6 mmol; 440 mg) were suspended in ACN (5 mL) in a sealed microwave tube and heated at 100°C in a microwave for 1h. The mixture was concentrated *in vacuo* to give **Precursor 56** (700 mg, 95%).

4-(2-((2-chloropyridin-4-yl)oxy)ethyl)morpholine (**Precursor 57**)		^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.18 (d, J= 6.0 Hz, 1H), 7.12 (d, J= 2.0 Hz, 1H), 6.99-7.01 (m, 1H), 4.19-4.22 (t, J= 5.60 Hz, 2H), 3.55-3.57 (t, J= 4.80 Hz, 4H), 2.61 (t, J= 6.40 Hz, 2H) and 2.45-2.50 (m, 4H). MS 243.09 $[M+H]^+$.

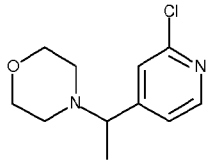
To an ice-cold solution of 2-chloropyridin-4-ol (1.0 g, 7.72 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (1.16 g, 7.72 mmol) in DMF (10 mL) was added K_2CO_3 (3.20 g, 23.16 mmol). The mixture was stirred at RT for 16 h. H_2O (20 mL) was added followed by extraction with EtOAc (3 x 100 mL). The combined organic layer were washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified on silica eluting with 5%MeOH: DCM to obtain **Precursor 57** (0.60 g, 33%).

The following precursor(s) were similarly prepared.

4-[3-[(2-chloro-4-pyridyl)oxy]propyl]morpholine (**Precursor 58**)		1H-NMR (400 MHz, DMSO-d_6): δ 8.18 (d, J= 6.0 Hz, 1H), 7.10 (d, J= 2.0 Hz, 1H), 6.98-7.10 (dd, J= 2.0 Hz and 5.60 Hz respectively, 1H), 4.13 (t, J= 6.40 Hz, 2H), 3.55-3.57 (t, J= 4.80 Hz, 4H), 2.34-2.40 (m, 6H) and 1.83-1.90 (m, 2H).
2-chloro-4-(tetrahydrofuran-2-ylmethoxy)pyridine (**Precursor 59**)		MS 214.08 $[M+H]^+$.
2-chloro-4-(2-methoxyethoxy)pyridine (**Precursor 60**)		1H NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, J= 5.60 Hz,1H), 6.88 (s, 1H), 6.79 (d, J= 5.60 Hz, 1H), 4.17 (m, 2H), 3.76 (m, 2H) and 3.43 (s, 3H).
4-[2-[(6-chloro-3-		MS 243.11 $[M+H]^+$.

pyridyl) oxy]ethyl] morpholine **(Precursor 61)**		
2-((2-chloropyrimidin-4-yl)amino)ethanol: **(Precursor 62)**		^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.96 (br s, 1H), 7.87 (d, *J*= 5.60 Hz, 1H), 6.48 (d, *J*= 5.60 Hz, 1H), 4.81 (m, 1H) and 3.52 (m, 4H). MS 174.01 $[M+H]^+$.

A solution of 2-chloro-*N*-(2-methoxyethyl)pyrimidin-4-amine (1.0 g, 5.34 mmol) in DCM (10 mL) was cooled to -10°C followed by drop wise addition of BBr_3 (0.70 mL, 8.02 mmol). The mixture was stirred at RT for 3 h. $NaHCO_3$ solution (5 mL) was added followed by extraction with DCM (2 x 50 mL). The combined organics were washed with H_2O, brine, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified on silica eluting with 80%EtOAc: Hexane to obtain **Precursor 62** as a white solid (0.35 g, 38%).

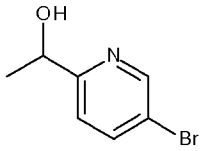
4-(1-(2-chloropyridin-4-yl)ethyl)morpholine **(Precursor 63)**		^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.36 (d, *J*= 5.20 Hz, 1H), 7.44 (s, 1H), 7.37 (d, *J*= 4.80 Hz, 1H), 3.55 (m, 4H), 3.47 (q, *J*= 6.80 Hz, 1H), 2.24-2.39 (m, 4H) and 1.27 (d, J= 6.80 Hz, 3H).

*1-(2-chloropyridin-4-yl)ethanol (**i**):* To an ice-cold solution of 1-(2-chloro-4-pyridyl)ethanone (1.0 g, 6.42 mmol) in MeOH was added $NaBH_4$ (0.73 g, 19.21 mmol) and the solution stirred at RT for 30 min. The reaction was then quenched with saturated NH_4Cl solution followed by extraction with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated in vacuo to obtain **i** (0.61 g, 60%). MS 158.10 $[M+H]^+$.

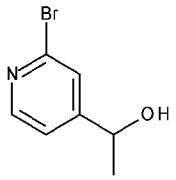
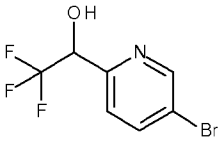
*1-(2-chloropyridin-4-yl)ethyl methanesulfonate (**ii**):* To an ice-cold solution of **i** (0.25 g, 1.58 mmol) in DCM (10 mL) was added Et_3N (0.43 mL, 3.16 mmol) and the resulting solution was stirred for 15 min at the same temperature followed by addition of methanesulfonyl chloride (0.18 mL, 2.37 mmol). The mixture was stirred at RT for 4 h. The reaction was quenched with H_2O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated in vacuo to obtain **ii** (0.30 g, 80%). MS 236.38 $[M+H]^+$.

*4-(1-(2-chloropyridin-4-yl)ethyl)morpholine (**Precursor 63**):* To an ice-cold solution of **ii** (0.30 g, 1.33 mmol) in DMSO (5 mL) was added powdered KOH (0.11 g, 1.99 mmol). The mixture was stirred at 0°C for 15 min followed by addition of morpholine

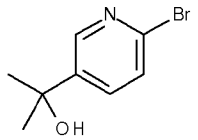
(0.23 g, 2.66 mmol) and the mixture then stirred at RT for 16 h. Ice-cold H_2O was added to the reaction mass followed by extraction with EtOAc (3 x 100 mL). The combined organic layer were washed with brine, dried (Na_2SO_4) and evaporated in vacuo to obtain **Precursor 63** (0.28 g, 93%).

1-(5-bromopyridin-2-yl)ethanol (**Precursor 64**)		^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.59 (m, 1H), 8.03 (d, *J*= 8.40 Hz, 1H), 7.49 (d, *J*= 8.40 Hz, 1H), 5.50 (d, *J*= 4.40 Hz, 1H), 4.69 (m, 1H), 1.34 (d, *J*= 6.40 Hz, 3H).

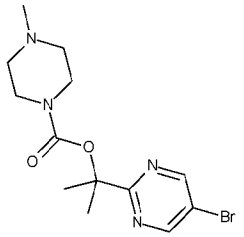
To an ice-cold solution of 5-bromopyridine-2-carbaldehyde (1.0 g, 5.37 mmol) in THF (10.0 mL) was added methyl magnesium bromide (3.44 mL, 6.88 mmol, 2M in Et_2O). The resulting reaction mixture was stirred at RT for 16 h. H_2O (100 mL) was added followed by extraction with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified over silica (50% EtOAc-hexanes) to obtain **Precursor 64** (0.80 g, 74%). The following precursor(s) were similarly prepared.

1-(2-bromo-4-pyridyl)ethanol (**Precursor 65**)		MS 202 $[M+H]^+$.
1-(5-bromopyridin-2-yl)-2,2,2-trifluoroethanol (**Precusor 66**)		^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.73 (m, 1H), 8.17 (dd, *J*= 2.0 and 8.40 Hz, 1H), 7.60 (d, *J*= 8.40 Hz, 1H), 7.16 (d, *J*= 6.0 Hz, 1H) and 5.15 (m, 1H). MS 255.88 $[M+H]^+$.

To an ice-cold solution of 5-bromopyridine-2-carbaldehyde (0.5 g, 2.69 mmol) in THF (10 mL) was added trimethyl(trifluoromethyl)silane (0.57 g, 4.03 mmol) followed by TBAF (6.73 mL, 6.73 mmol, 1.0 M THF). The mixture was stirred at RT for 16 h. H_2O (100 mL) was added followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo The residue was purified over silica (20% EtOAc-hexanes) to obtain **Precursor 66** (0.61 g, 89%).

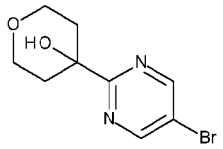
2-(6-bromo-3-pyridyl)propan-2-ol (**Precursor 67**)	 MS 216 $[M+H]^+$.

To a solution of 1-(6-bromo-3-pyridyl)ethanone (500 mg, 2.68 mmol) in THF (20 mL) to 0 °C was added methyl magnesium bromide (3 M in diethylether, 1.2 mL, 3.7 mmol) dropwise and the mixture allowed to warm to RT and stirred for 60 min. The mixture was re-cooled to 0 °C and $NaHCO_3$ solution (100 mL) added. The mixture was extracted with EtOAc (100 mL). The organic layer was separated and the aqueous layer extracted with a further portion of EtOAc (100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography, on silica eluting with 0-5% methanol in DCM, followed by further chromatography, on silica eluting with 0-50% EtOAc in n-heptane, gave **Precursor 67**.

2-(5-bromopyrimidin-2-yl)propan-2-yl 4-methylpiperazine-1-carboxylate (**Precursor 68**)	 MS 344.87 & 342.87 $[M+H]^+$.

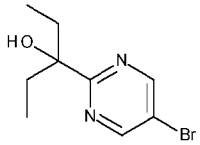
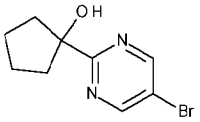
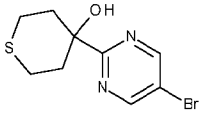
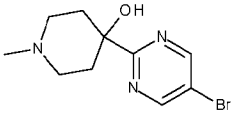
*2-(5-bromopyrimidin-2-yl)propan-2-yl 4-nitrophenyl carbonate (**i**):* Sodium hydride (110 mg, 2.8 mmol) was added to a solution of **Precursor 1** in THF (10 ml) at 0°C and stirred for 1 h. To this mixture was added 4-nitrophenyl carbonochloridate (560 mg, 2.8 mmol) portionwise and the solution was stirred at 0°C for 1 h.. EtOAc (3 ml) and H_2O were added, the organic layer separated, dried and concentrated to give **i** (900 mg).

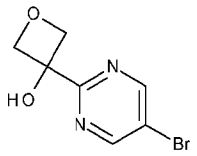
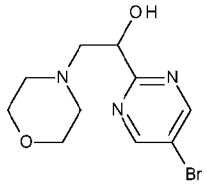
*2-(5-bromopyrimidin-2-yl)propan-2-yl 4-methylpiperazine-1-carboxylate (**Precursor 68**):* 1-methylpiperazine (1.05 g, 10.47 mmol) was added to a solution of **i** (1 g, 2.1 mmol) in DMF (10 mL) and stirred at RT for 18 h. The mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (20 mL) and H_2O (10 mL), the organic layer was separated and washed with further H_2O (2 x5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by chromatography on silica, eluting with 0-10% MeOH/DCM) gave **Precursor 68** (144 mg, 20%).

4-(5-bromopyrimidin-2-yl)tetrahydro-2*H*-pyran-4-ol (**Precursor 69**)	 MS 258.92 & 260.88 $[M+H]^+$.

5-Bromo-2-iodo-pyrimidine (1.14 g, 4 mmol) in toluene (4 mL) was added dropwise to a solution of n-BuLi (2.76 mL 1.52 M) in toluene (8mL) at -78 °C. After stirring at -78 °C for 1 h, and tetrahydro-4H-pyran-4-one (1.6 g, 1.5 mL, 16 mmol) which had been dried over 3Å molecular sieves for >30 mins, was added in one portion with vigorous stirring. The reaction allowed to warm to RT and stirred for 3 h. The reaction was quenched with NH_4Cl (10 mL), and extracted with EtOAc (4 x 20mL). The organic layers were combined, dried (Na_2SO_4), concentrated in vacuo. The residue was purified by flash chromatography (10%-45% EtOAc in heptane) to give **Precursor 69** (535mg, 53%).

The following precursor(s) were similarly prepared.

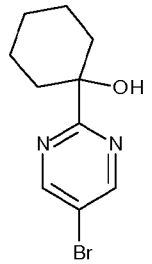
3-(5-bromopyrimidin-2-yl)pentan-3-ol **(Precursor 70)**	 MS 244.86 $[M+H]^+$.
1-(5-bromopyrimidin-2-yl)cyclopentanol **(Precursor 71)**	 MS 242.88 $[M+H]^+$.
4-(5-bromopyrimidin-2-yl)tetrahydrothiopyran-4-ol **(Precursor 72)**	 MS 276.91 $[M+H]^+$.
4-(5-bromopyrimidin-2-yl)-1-methyl-piperidin-4-ol **(Precursor 73)**	 MS 272.02 $[M+H]^+$.

3-(5-bromopyrimidin-2-yl)oxetan-3-ol **(Precursor 74)**	 MS 230.96 & 232.94 $[M+H]^+$.
1-(5-bromopyrimidin-2-yl)-2-morpholino-ethanol (**Precursor 75**)	 MS 288.05 & 290.01 $[M+H]^+$.

*5-bromo-2-vinyl-pyrimidine (**i**):* 5-Bromo-2-iodo-pyrimidine (2.15 g, 7.55 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.60 mL, 9.43 mmol) and $PdCl_2(dppf)^{\cdot}$ (300 mg, 0.40 mmol) were dissolved in 1,4-dioxane (15 mL). A solution of Cs_2CO_3 (4.91 g, 15.1 mmol) in H_2O (5 mL) was added and the mixture heated at 80 °C for 30 min. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O, brine and separated. The organic fraction was dried and concentrated in vacuo. Purification by chromatography on silica, eluting with 5-25% EtOAc/heptane gave **i** (1.10 g, 79%). MS 185.11 & 187.09 $[M+H]^+$.

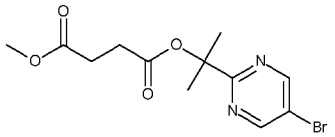
*5-bromo-2-(oxiran-2-yl)pyrimidine (**ii**):* Acetic acid (680 µL, 11.9 mmol) and **i** (1.1 g, 5.95 mmol) were dissolved in 1,4-dioxane (30 mL) and H_2O (80 mL). The solution was cooled to 0 °C and NBS (1.27 g, 7.13 mmol) added portion-wise. The reaction was allowed to warm to RT, then 2M NaOH (50 mL) was added and stirring was continued for 16 h. The reaction was diluted with H_2O and extracted with EtOAc. The organic fraction was washed with brine and dried (Na_2SO_4). Purification by chromatography on silica, eluting with 10-50% EtOAc/heptane gave **ii** (140 mg, 12%). MS 200.92 & 202.91 $[M+H]^+$.

*1-(5-bromopyrimidin-2-yl)-2-morpholino-ethanol (**Precursor 75**):* A solution of **ii** (140 mg, 0.70 mmol) in morpholine (2.0 mL) was heated at 120 °C under microwave irradiation for 1 h. Concentration to dryness under a stream of N_2 afforded **Precursor 75**.

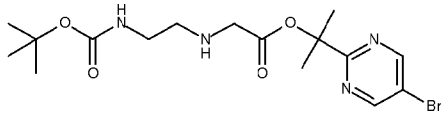
1-(5-bromopyrimidin-2-yl)cyclohexanol (**Precursor 76**)	 MS 257.0 & 259.0; 1:1 $[M+H]^+$.

Methyl 5-bromopyrimidine-2-carboxylate (250 mg; 1.15 mmol) was dissolved in anhydrous THF (10 mL) and cooled to 0°C. Pentamethylenebis(magnesium bromide) (0.5 M in THF 3.0 mL, 1.3 mmol) was introduced drop-wise and the mixture stirred for 15 min. The reaction was quenched with MeOH (0.5 mL), partitioned with EtOAc (100 mL), washed with H_2O (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica, eluting with 0-100%, EtOAc in *n*-heptane gave **Precursor 76** (7%).

It will be understood that esters of any of the preceding Precursor(s) may be formed as illustrated by the following example(s).

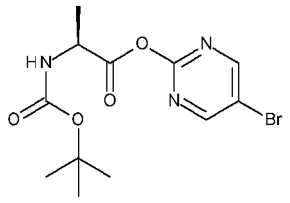
*O*4-[1-(5-bromopyrimidin-2-yl)-1-methyl-ethyl] O1-methyl butanedioate (**Precursor 77**)	 MS 330.79 & 332.83 $[M+H]^+$.

Precursor 1 (8.0 g, 36.9 mmol) was dissolved in anhydrous DMF (80 mL) under argon and cooled in an ice bath. Sodium hydride (1.62 g, 60% in mineral oil, 40.5 mmol) was added portion-wise and the reaction stirred for 10 min. Methyl 4-chloro-4-oxobutyrate (13.6 mL, 111 mmol) was added and the mixture warmed to RT. More methyl 4-chloro-4-oxobutyrate (4.50 mL, 36.9 mmol) was added after 18 h and stirring continued. Further methyl 4-chloro-4-oxobutyrate (4.50 mL, 36.9 mmol) was added after 25.5 h and stirring continued. The mixture was quenched with H_2O after 45 h, then cooled in an ice bath and basified to pH 9 with $NaHCO_3$ (sat., aq.) solution. The mixture was extracted into EtOAc (4 x 200 mL). The combined organic phases were washed with H_2O and brine, dried (Na_2SO_4) and concentrated to dryness in vacuo to give an oil. The mixture was purified by chromatography, Biotage SP4, 120 g Si cartridge, 0-20% EtOAc in cyclohexane to give **Precursor 77**, 8.02 g (66%).

[1-(5-bromopyrimidin-2-yl)-1-methyl-ethyl] 2-[2-(tert-butoxycarbonyl amino) ethylamino] acetate (**Precursor 78**)	 MS 292.69, 294.68 and 296.69 $[M+H]^+$.

*[1-(5-bromopyrimidin-2-yl)-1-methyl-ethyl] 2-chloroacetate (**i**):* **Precursor 1** (1.03 g, 4.75 mmol) was dissolved in anhydrous DMF (15 mL) under argon. Sodium hydride (209 mg, 60% in mineral oil, 5.22 mmol) was added and the mixture stirred for 15 min. Chloroacetyl chloride (1.13 mL, 14.2 mmol) was added and the mixture stirred at RT. After 18 h, chloroacetyl chloride (1.13 mL, 14.2 mmol) was added and stirring continued. The mixture was quenched with H_2O after 42 h and extracted into EtOAc (4 x 50 mL). The combined organic phases were washed with H_2O and brine, dried (Na_2SO_4) and concentrated to dryness in vacuo. Purification by chromatography on silica, eluting with 0-20% EtOAc in n-heptane gave **i** (930 mg, 67%).

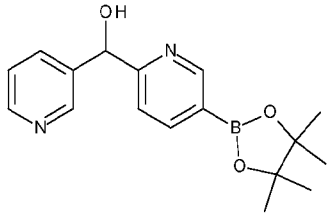
*[1-(5-bromopyrimidin-2-yl)-1-methyl-ethyl] 2-[2-(tert-butoxycarbonylamino) ethylamino]acetate (**Precursor 78**):* DMAP (4 mg, 0.03 mmol) and **i** (97 mg, 0.33 mmol) were dissolved in anhydrous THF (5 mL) under argon and DIPEA (0.09 mL, 0.50 mmol) and *N*-Boc-ethylenediamine (0.06 mL, 0.40 mmol) added. The mixture was stirred at RT for 1 h then warmed to 50 °C for 17 h. More DIPEA (0.09 mL, 0.50 mmol), DMAP (4 mg, 0.03 mmol) and *N*-Boc-ethylenediamine (0.06 mL, 0.40 mmol) were added and the temperature raised to 60 °C. After 30 h, the mixture was cooled to RT, quenched with H_2O and extracted into EtOAc (4 x 10 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated to dryness in vacuo to give **Precursor 78** (191 mg). MS 416.97 and 418.95 $[M+H]^+$.

(5-bromopyrimidin-2-yl) (2S)-2-(tert-butoxycarbonylamino)propanoate (**Precursor 79**)	 MS 387.82 and 389.81 $[M+H]^+$.

(2S)-2-(tert-Butoxycarbonylamino)propanoic acid (95 mg, 0.50 mmol), **Precursor 1** (109 mg, 0.50 mmol) and DMAP (61 mg, 0.50 mmol) were dissolved in THF (2 mL). DCC (104 mg, 0.50 mmol) was added last and the reaction was stirred at RT under argon for 16 h. Additional (2S)-2-(tert-butoxycarbonylamino)propanoic acid (95 mg, 0.50 mmol), DMAP (61 mg, 0.50 mmol) and DCC (104 mg, 0.50 mmol) were added

and the reaction stirred at RT for 16 h. The reaction was filtered and washed with THF and the filtrate concentrated in vacuo. Purification by chromatography on silica, eluting with 10-50% EtOAc/heptane, followed by purification by chromatography on silica, eluting with 0-10% MeOH/DCM gave **Precursor 79** (148 mg, 76%).

It will be understood that boronic acid and esters thereof e.g. boronates such as 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl and 5,5-dimethyl-1,3,2-dioxoaborinan-2-yl, of any of the preceding Precursor(s) may be formed as illustrated by the following example(s).

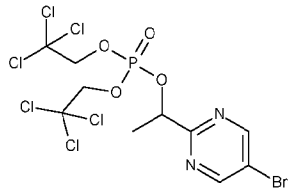
3-pyridyl-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]methanol (**Precursor 80**)	 MS 313.18 $[M+H]^+$.

*(5-Bromopyridin-2-yl)(pyridin-3-yl)methanone (**i**):* A solution of 3-bromopyridine (2.50 g, 15.82 mmol) in THF (25.0 mL) was cooled to -78°C followed by drop wise addition of n-BuLi (1.60 M in hexane, 11.90 mL, 18.98 mmol). The mixture was stirred at -78°C for 30 min followed by addition of methyl 5-bromopicolinate (4.10 g, 18.98 mmol) dissolved in minimum amount of THF at -78°C. The temperature of the reaction was slowly raised up to RT and then stirred overnight. The reaction was then cooled to 0°C and saturated NH_4Cl solution (50 mL) added followed by extraction with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified over silica eluting with 25% EtOAc-hexanes to obtain **i** (2.50 g, 60%). MS 263.09 $[M+H]^+$.

*(5-Bromopyridin-2-yl)(pyridin-3-yl)methanol (**ii**):* To an ice-cold solution of **i** (2.50 g, 9.50 mmol) in MeOH (25.0 mL) was added sodium borohydride (1.05 g, 28.50 mmol) portion wise. The resulting mixture was stirred at RT for 30 min, then H_2O (50 mL) was added followed by extraction with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated in vacuo to obtain **ii** (1.75 g, 70%). MS 265.11 $(M+H)^+$.

*3-pyridyl-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]methanol (**Precursor 80**):* To the solution of **ii** (0.50 g, 1.89 mmol) in 1,4-dioxane (10 mL) was added bis(pinacolato)diboron (0.53 g, 2.08 mmol) and KOAc (0.28 g, 2.84 mmol). The reaction was degassed by purging N_2 for 15 min followed by addition of

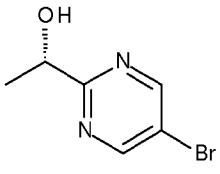
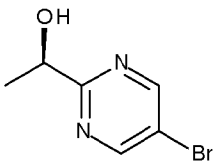
$Pd_2(dba)_3$ (0) (0.10 g, 0.10 mmol) and tricyclohexylphosphine (0.06 g, 0.23 mmol). The reaction was degassed for 10 min and heated up to 80°C for 2h. The resulting mixture was cooled to RT and filtered through a celite bed. The filtrate was concentrated in vacuo to obtain **Precursor 80** (0.41 g, 70%).

1-(5-bromopyrimidin-2-yl)ethyl bis(2,2,2-trichloroethyl) phosphate (**Precursor 81**)	 MS: 546.74 $[M+H]^+$.

N,N-dimethylpyridin-4-amine (120 mg) was added to a solution of bis(2,2,2-trichloroethyl)phosphorochloridate (450 mg) and **Precursor 4** (200 mg) in THF (10 mL) and the mixture heated at 70°C for 1 h. The mixture was cooled to RT and filtered. The filtrate was concentrated *in vacuo* and purified by chromatography on silica, eluting with 40%EtOAc/n-heptane -80%%EtOAc/n-heptane to give **Precursor 81** (300mg, 56%).

It will be understood that any of the preceding Precursor(s) having a chiral alcohol may be synthesised from an enatiomeric resolving agent and/or separated into their respective enantiomers by suitable chiral separation methods known to those in the art such as chiral HPLC as illustrated by the following example(s).

<u>(1S)-1-(5-bromopyrimidin-2-yl)ethanol (**Precursor 82**) and (1R)-1-(5-bromopyrimidin-2-yl)ethanol (**Precursor 83**)</u>


; and


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 2H); 4.92 (dq, J = 5.6, 6.8 Hz, 1H); 3.80 (1H, d, J = 5.6 Hz); 1.55 (t, J = 6.8 Hz, 3H).

1-(5-bromopyrimidin-2-yl)ethyl (2R)-2-(tert-butoxycarbonylamino)-3-methyl-butanoate (i): A mixture of **Precursor 4** (27.8 g, 137 mmol), Boc-D-valine (32.7 g, 151 mmol) and DMAP (10.0 g, 82.2 mmol) was dissolved in THF (200 mL). The mixture was cooled in an ice bath. A solution of DCC (31.1 g, 151 mmol) in THF (50 mL) was added. After 10 min, the cooling bath was removed. The mixture was stirred overnight, filtered, the DCU precipitate was washed with several portions of EtOAc,

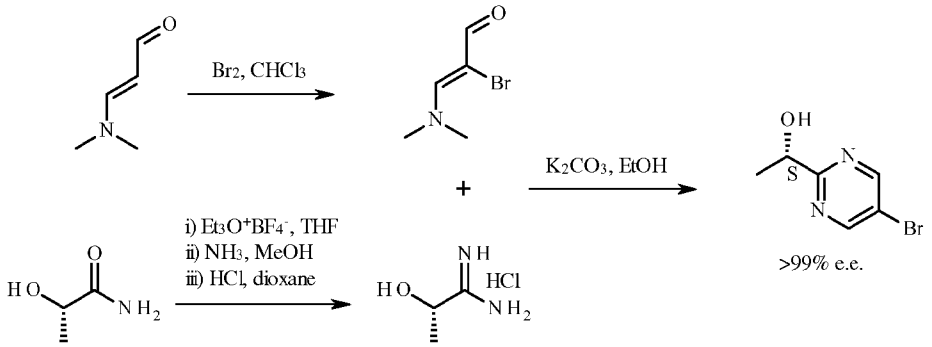
and the combined filtrates were concentrated. The residue was then eluted through a plug of silica (20% EtOAc/heptane) to give **i** (64.7 g).

*[(1S)-1-(5-bromopyrimidin-2-yl)ethyl] (2R)-2-(tert-butoxycarbonylamino)-3-methyl-butanoate (**ii**):* **i** (64.7 g) was crystallised from hot heptane. The solids obtained were collected by filtration and recrystallised from hot heptane, yielding **ii** (15.4 g).

*(1S)-1-(5-bromopyrimidin-2-yl)ethanol (**Precursor 82**):* Amberlite® basic ion exchange resin and **ii** (15.4 g, 38.3 mmol) were stirred in MeOH (50 mL) overnight at RT. The suspension was filtered through a pad of silica using 1:1 MeOH/DCM and the filtrate concentrated in vacuo. Crystallisation from hot heptane gave **Precursor 82** (5.85 g). *(1S)-1-(5-bromopyrimidin-2-yl)ethanol (**Precursor 83**)* was similarly prepared using Boc-L-valine. Mitsunobu inversion of one enantiomer to the desired enantiomer may also be employed.

Chiral HPLC was used to demonstrate the chiral purity of the enantiomers (Column: Chirapak IC, 0.46 cm x 25 cm; 20 min isocratic gradent; 5:95 EtOH:n-hexane + 0.1% diethylamine) retention time = 14.65 min / 17.53 min.

Alternatively, **Precursor 82** (S-enantiomer) may be synthesized as follows.



(Z)-2-bromo-3-(dimethylamino)prop-2-enal: (3-(Dimethylamino)acrolein (25 g) was dissolved in chloroform (250 mL), and the mixture cooled in an ice/water bath. bromine (40 g; 13 mL) was added dropwise and once the addition was complete, the reaction was allowed to warm to room temperature and stirred for 1 hour. The reaction was diluted with DCM (150 mL) and quenched by the addition of aq. sat Na_2SO_5 solution (50 mL) and aq. sat. $NaHCO_3$ solution (250 mL). The organic layer was collected and dried ($MgSO_4$) and the solvent removed in vacuo. Once the material had solidified, it was suspended in ethyl acetate: heptane (1:1 - 100 mL) and the resulting solid material collected by filtration. Washing with ethyl acetate: heptane and air drying gave (Z)-2-bromo-3-(dimethylamino)prop-2-enal as a fawn coloured

solid (25g, 75%). ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1H), 7.2 (s, 1H), 3.36 (s, 6H).

(2S)-2-hydroxypropanamidine hydrochloride hydrochloride salt: (2S)-2-hydroxypropanamide (20 g) was placed in a flask with THF (100 mL) and triethyloxonium tetrafluoroborate (47 g) was added and the mixture stirred for 1 hour. The solvent was removed and the residue dissolved in methanol (100 mL) and ammonia (7M in methanol) (150 mL) added over ~10 mins cooling the reaction mixture in a cold water bath. Once the addition was complete the reaction was allowed to warm to room temperature. The resulting suspension was concentrated to a thick mixture, diluted with ethyl acetate and filtered through celite. The filtrate was cooled to ~10°C and HCl (4M in dioxane) (100 mL) added dropwise. After stirring for 90 mins, the mixture was filtered to collect the white precipitate (washing with ethyl acetate and then dried in a vacuum oven at 40°C to give (2S)-2-hydroxypropanamidine hydrochloride hydrochloride salt as a white solid (12 g, 43%). ^{1}H NMR ($CDCl_3$) δ 8.8 (m, 4H), 6.26 (s, 1H), 4.43 (q, J = 6.7 Hz, 1H), 1.35 (d, J = 6.7 Hz, 3H).

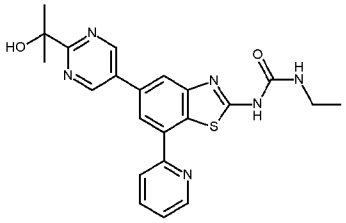
(1S)-1-(5-bromopyrimidin-2-yl)ethanol: (Z)-2-bromo-3-(dimethylamino)prop-2-enal (11.5 g), potassium carbonate (13.4 g), ethanol (200 mL) and 2-hydroxy-2-methyl-propanamidine hydrochloride (12.1 g) were placed in a flask and the mixture heated at 85°C overnight. The reaction mixture was cooled and the mixture filtered, washed with ethanol and the combined filtrates concentrated *in vacuo* with silica gel. This residue was purified by chromatography on silica, eluting with 0-50% ethyl acetate in heptane to give (1S)-1-(5-bromopyrimidin-2-yl)ethanol as a white solid (2.1g, 16%). ^{1}H NMR ($CDCl_3$) δ 8.83 (s, 2H), 4.98 (m, 1H), 3.8 (m, 1H), 1.6 (d, J = 6.6 Hz, 3H). Chiral HPLC: Column: Chirapak IC, 0.46 cm x 25 cm; 20 min isocratic gradent; 5:95 EtOH:n-hexane + 0.1% diethylamine) retention time = 14.08 min. (racemic mixture: ~14.5 min: S isomer ; ~17.5 min: R isomer).

Precursor 83 (R-enantiomer) may be formed using R-lactamide.

Once formed, **Precursor 82** or **Precursor 83** may be coupled to an Intermediate core then optionally subjected to Mitsunobu inversion conditions to obtain the other enantiomeric form, if desired.

Example(s) of General Method A

1-Ethyl-3-(5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7-(pyridin-2-yl)benzo[d]thiazol-2-yl)urea (**1**)

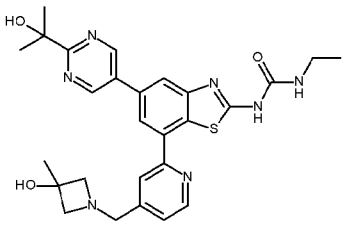


^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 2H), 8.77 (d, J = 4.1 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.93 (t, J = 8.7 Hz, 1H), 7.91 - 7.77 (m, 2H), 7.35 - 7.29 (m, 1H), 3.44 - 3.31 (m, 3H), 1.66 (s, 6H), 1.32 - 1.15 (m, 4H). MS: 435.1 $[M+H]^+$.

Precursor 1 (50 mg) was placed in a flask with **Intermediate 1** (100 mg), Cs_2CO_3 (67 mg), Pd(dppf)Cl_2 (16 mg), DMF (3 mL) and H_2O (0.5 mL) and the mixture heated at 85°C for 16 h. The mixture was cooled to RT and partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic layer was collected and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by chromatography on silica, eluting with a gradient of 0 - 10 % MeOH in DCM gave Compound **1** (12 mg).

The following compound(s) were similarly prepared noting that alternative catalysts, bases, solvents and reaction times may be employed and the urea may require protection as a 5-methyl-1,3,5-triazinan-2-one.

<u>1-Ethyl-3-(7-(4-((3-hydroxy-3-methylazetidin-1-yl)methyl)pyridin-2-yl)-5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)benzo[d]thiazol-2-yl)urea (**2**)</u>



^{1}H NMR (DMSO-d_6): δ 10.61 (br s, 1H), 9.33 (s, 2H), 8.72 (d, J= 5.20 Hz, 1H), 8.34 (m, 2H), 8.12 (s, 1H), 7.36 (m, 1H), 6.84 (m, 1H), 5.21 (s, 1H), 5.15 (s, 1H), 3.74 (s, 2H), 3.17-3.26 (m, 4H), 2.97-2.99 (m, 2H), 1.57 (s, 6H), 1.38 (s, 3H) and 1.09 (t, J=7.20 Hz, 3H). MS: 534.32 $[M+H]^+$.

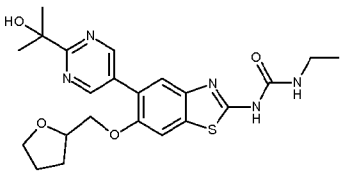
*1-(7-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)benzo[d]thiazol-2-yl)-3-ethyl-5-methyl-1,3,5-triazinan-2-one (**i**)*: To a solution of **Intermediate 4** (0.25 g, 0.51 mmol) in toluene (10 mL) was added bis(neopentylglycolato) diboron (0.23 g, 1.01 mmol) and potassium acetate (0.15 g, 1.53 mmol). The reaction mass was degassed by purging N_2 for 15 min followed by addition of Pd(dppf)Cl_2 (0.041 g, 0.091 mmol). The mixture was degassed for 10-15 min and then heated at 130°C for 30 min.The mixture was cooled to RT and filtered through celite. The filtrate was concentrated in vacuo to obtain **i** (0.21 g, 80% crude). MS: 455.20 $[M-H]^+$, (MS of corresponding boronic acid observed).

*1-Ethyl-3-(7-(4-((3-hydroxy-3-methylazetidin-1-yl)methyl)pyridin-2-yl)-5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)benzo[d]thiazol-2-yl)-5-methyl-1,3,5-triazinan-2-one (**ii**):* To a solution of **i** (0.427 g, 0.81 mmol) in 1,4-dioxane-H_2O (9:1, 10 mL) was

added **Precursor 29** (0.231 g, 0.90 mmol) and Cs_2CO_3 (0.791 g, 2.43 mmol). The reaction mixture was degassed by purging N_2 for 15 min followed by addition of $Pd(dppf)Cl_2$ (0.066 g, 0.08 mmol). The mixture was heated in a microwave at 110°C for 30 min. The mixture was diluted with H_2O and extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified over silica eluting with 7% MeOH: DCM to obtain **ii** (0.303 g, 63%). ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.34 (s, 2H), 8.75 (d, J= 4.40 Hz, 1H), 8.38 (m, 2H), 8.20 (s, 1H), 7.37 (m, 1H), 5.23 (br s, 1H), 5.15 (s, 3H), 4.38 (s, 2H), 3.75 (br s, 2H), 3.38 (m, 2H), 3.26 (m, 2H), 2.94 (m, 2H), 2.55 (s, 3H), 1.57 (s, 6H), 1.38 (s, 3H), and 1.12 (t, J= 7.20 Hz, 3H). MS: 589.31 $[M+H]^+$.

*1-ethyl-3-(7-(4-((3-hydroxy-3-methylazetidin-1-yl)methyl)pyridin-2-yl)-5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)benzo[d]thiazol-2-yl)urea (**2**)* : An ice-cold solution of **ii** (0.25 g, 0.42 mmol) in MeOH-DCM (0.50 and 10 mL respectively) was purged with HCl (g) for 10 min and the mixture stirred at RT for 16 h. The solvent was evaporated and the residue triturated with a mixture of MeOH and Et_2O to obtain Compound **2** (0.225 g, 90%).

<u>1-Ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(tetrahydrofuran-2-ylmethoxy)-1,3-benzothiazol-2-yl]urea (**3**)</u>



^{1}HNMR (DMSO-d_6, 400 MHz): δ 10.63 (br s, 1H), 9.00 (s, 2H), 7.72 (m, 2H), 6.68 (m, 1H), 5.12 (s, 1H), 4.21 (m, 1H), 4.06 (m, 2H), 3.68 (m, 2H), 3.18 (m, 2H), 1.94 (m, 1H), 1.71 (m, 2H), 1.65 (m, 1H), 1.61 (s, 6H) and 1.22 (t, *J*= 6.8 Hz, 3H). LCMS: 458.20 $[M+H]^+$.

*2-((2-Bromo-4-nitrophenoxy)methyl)tetrahydrofuran (**i**):* To an ice cold solution of 2-bromo-1-fluoro-4-nitro-benzene (5.0 g, 22.72 mmol) in DMSO (40 mL) was added NaOH (1.36 g, 34.09 mmol) and (tetrahydrofuran-2-yl)methanol (3.47 g, 34.09 mmol) at 0°C. The mixture was stirred at RT for 1 h, then poured into H_2O (50 mL), the pH adjusted ~7 with 1M HCl and extracted with EtOAc (2 x 250 mL). The combined organics were washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated in vacuo to obtain **i** (6.50 g, 95%).^{1}HNMR ($CDCl_3$, 400 MHz): δ 8.46 (d, *J*= 2.40 Hz, 1H), 8.20 (dd, *J*= 2.40 and 9.20 Hz respectively, 1H), 6.98 (d, *J*= 9.20 Hz, 1H), 4.36 (m, 1H), 4.16 (m, 2H) 3.97 (m, 1H) 3.86 (m 1H) 2.07 (m 2H) and 1.95 (m 2H).

*3-Bromo-4-((tetrahydrofuran-2-yl)methoxy)aniline (**ii**):* To the solution of **i** (5.5 g, 18.2 mmol) in THF (30 mL) was added stannous chloride dihydrate (12.3 g, 54.6

mmol) at RT. The mixture was stirred at 60°C for 5 h. The mixture was poured into saturated sodium bicarbonate solution (100 mL) and extracted with EtOAc (2 x 500 mL). The combined organics were washed with H_2O, brine, dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified over silica (50% EtOAc:Hexanes) to obtain **ii** (4.0 g, 82%). MS: 272.0 $[M+H]^+$.

*5-bromo-6-((tetrahydrofuran-2-yl)methoxy)benzo[d]thiazol-2-amine (**iii**):* To a solution of **ii** (3.0 g, 11.62 mmol) in acetic acid (50 mL) was added ammonium thiocynate (4.18 g, 55.11 mmol) at RT. The resulting mixture was stirred at RT for 15 min followed by the addition of bromine (0.68 mL, 13.22 mmol) in acetic acid (5 mL). The mixture was stirred at RT for 5 h. The pH was adjusted to >7 with ammonia solution followed by extraction with EtOAc (2 x 200 mL). The combined organics were washed with H_2O, brine solution, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified over silica (60% EtOAc-Hexanes) to obtain **iii** (1.0 g, 26%). ^{1}HNMR (DMSO-d_6, 400 MHz): δ 7.50 (s, 1H), 7.49 (s, 1H), 7.43 (br s, 2H), 4.18 (m, 1H), 3.96 (m, 2H), 3.80 (m, 1H), 3.69 (m, 1H), 1.96 (m, 2H) and 1.78 (m, 2H). MS: 329.0 $[M+H]^+$.

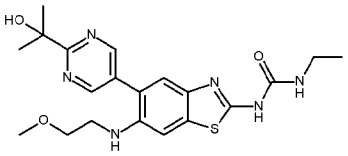
*1-(5-Bromo-6-((tetrahydrofuran-2-yl)methoxy)benzo[d]thiazol-2-yl)-3-ethylurea (**iv**):* To a solution of **iii** (1.0 g, 3.03 mmol) in 1,4-dioxane (10 mL) was added ethyl isocynate (1.23 mL, 15.19 mmol) at RT. The mixture was stirred at 80°C for 5 h. The reaction mixture was evaporated in vacuo, H_2O (50 mL) added to and the mixture stirred at 70°C for 4 h. The residue was filtered and dried under vacuum to obtain **iv** (1.0 g, 83%). ^{1}HNMR (DMSO-d_6, 400 MHz): δ 10.69 (br s, 1H), 7.80 (s, 1H), 7.68 (s, 1H), 6.65 (m, 1H), 4.21 (m, 1H), 4.04 (m, 2H), 3.83 (m, 1H), 3.70 (m, 1H), 3.16 (m, 2H), 2.0 (m, 2H), 1.82 (m, 2H) and 1.09 (t, J= 7.20 Hz, 3H). MS:400 $[M+H]^+$.

*1-Ethyl-3-(5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-6-((tetrahydrofuran-2-yl)methoxy)benzo[d]thiazol-2-yl)urea (**3**):* To a solution of **iv** (0.303 g, 0.75 mmol) and the 4,4,5,5-tetramethyl-1,3,2-dioxaborolon-2-yl) ester of **Precursor 1** (0.20 g, 0.75 mmol) in 1,4-dioxane : MeOH (5:3, 8.0 mL) was added potassium phosphate (0.24 g, 1.13 mmol) at RT. The mixture was degassed for 15-20 min by purging N_2 followed by the addition of Pd(dppf)Cl_2 (0.062 g, 0.075 mmol). The mixture was degassed for 15-20 min and heated at 80°C for 5 h. The reaction mixture was cooled to RT, diluted with EtOAc (500 ml) and filtered through celite. The filtrate was

evaporated in vacuo and the crude residue was purified over silica (5% MeOH-DCM) to obtain Compound **3** (0.15 g, 43%).

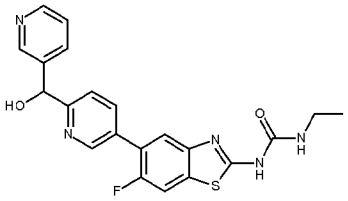
1-Ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-methoxyethylamino)-1,3-benzothiazol-2-yl]urea (**150**)

Compound **150** was similarly prepared to Compound **3**, starting from 1-[5-bromo-6-(2-methoxyethylamino)-1,3-benzothiazol-2-yl]-3-ethyl-urea and 2-methoxyethanamine.



^{1}H NMR (400 MHz; DMSO-d_6): δ 10.46 (br s, 1H), 8.85 (s, 2H), 7.34 (s, 1H), 7.23 (s, 1H), 6.65 (m, 1H), 5.13 (br s, 1H), 4.87 (m, 1H), 3.48 (m, 2H), 3.17-3.24 (m, 7H), 1.55 (s, 6H), and 1.08 (m, 3H). MS 431.16 $[M+H]^+$

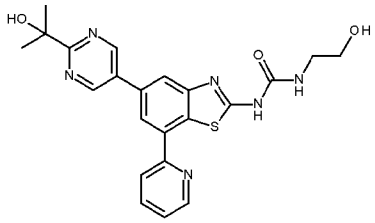
1-Ethyl-3-(6-fluoro-5-(6-(hydroxy(pyridin-3-yl)methyl)pyridin-3-yl)benzo[d]thiazol-2-yl)urea (**4**)



^{1}H NMR (400 MHz; DMSO-d_6): δ 8.67 (m, 2H), 8.45 (d, *J*= 3.60 Hz, 1H), 8.05 (m, 1H), 7.95 (m, 1H), 7.73-7.81 (m, 3H), 7.35 (m, 1H), 6.74 (m, 1H), 6.36 (d, *J*= 4.0 Hz, 1H), 5.85 (d, *J*= 4.0 Hz, 1H), 3.38 (m, 1H), 3.21 (m, 2H) and 1.08 (t, *J*= 7.20 Hz, 3H). MS: 424.31 $[M+H]^+$

To a solution of **Precursor 80** (0.2 g, 0.6 mmol) in 1,4-dioxane (5 mL) and MeOH (3 mL) was added **Intermediate 13** (0.2 g, 0.6 mmol) and potassium phosphate (0.2 g, 0.96 mmol). The reaction mass was degassed by purging N_2 for 15 min followed by addition of Pd(dppf)Cl_2 (0.05 g, 0.06 mmol). The mixture was degassed for 10 min and heated at 80°C for 4 h. The solvent was evaporated, H_2O (50 mL) added and the mixture extracted with EtOAc (4 x 50 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified over silica eluting with 2.50 % MeOH in DCM to obtain Compound **4** (0.02 g, 10%).

1-(2-Hydroxyethyl)-3-(5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7-(pyridin-2-yl)benzo[d]thiazol-2-yl)urea (**5**)



^{1}H NMR (400 MHz; CD_3OD) δ = 9.14 (s, 2H), 8.70 (d, *J* = 4.3 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.10 (s, 1H), 7.97 -7.82 (m, 2H), 7.42 -7.25 (m, 1H), 3.75 (t, *J* = 5.5 Hz, 2H), 3.46 (t, *J* = 5.5 Hz, 2H), 1.69 (s, 6H). MS: 451.08 $[M+H]^+$

[2-amino-7-(2-pyridyl)-1,3-benzothiazol-5-yl] trifluoromethanesulfonate (i): [2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]

trifluoromethanesulfonate (1.34 g, 3.0 mmol) was dissolved in DMSO (10 mL) and stirred at 160 °C for 16 h. The mixture was diluted with EtOAc, washed with H_2O, brine. The organic fraction was concentrated in vacuo to afford **i** (1.01 g, 90%). MS: 375.96 $[M+H]^+$.

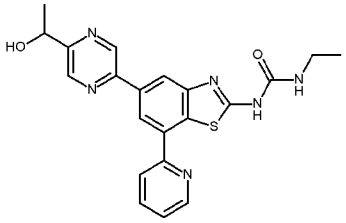
*[2-(2-hydroxyethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl] trifluoromethanesulfonate (**ii**):* Compound **i** (445 mg, 1.18 mmol) was dissolved in DMF (7 mL) and solution of CDI (577 mg, 3.56 mmol) in DMF (3 mL) was added drop-wise at 0 °C with stirring under argon. The mixture was warmed to RT and stirred for 16 h. A solution of ethanolamine (710 µL, 11.85 mmol) in DMF (2 mL) was then added and the mixture stirred at RT for 4 h. The mixture was diluted with EtOAc, washed with H_2O, brine. The organic fraction was dried (Na_2SO_4) and concentrated in vacuo. The residue was washed with MeOH and Et_2O to afford **ii** (253 mg, 46%). MS: 463.00 $[M+H]^+$.

*2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]propan-2-ol (**iii**):* **Precursor 1** (140 mg, 0.645 mmol), bispinacolatodiboron (197 mg, 0.774 mmol) and potassium acetate (95 mg, 0.967 mmol) were suspended in anhydrous 1,4-dioxane (5 mL). Tricyclohexylphosphine (23 mg, 0.081 mmol) and $Pd_2(dba)_3$ (30 mg, 0.032 mmol) were added and the mixture degassed/purged with argon (x3). The reaction mixture was stirred at 100 °C under microwave irradiation for 1 h. The reaction was cooled to RT, filtered and washed with 1,4-dioxane (5 mL) to give **iii**. MS: 182.96 $[M+H]^+$ (boronic acid).

*1-(2-hydroxyethyl)-3-(5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7-(pyridin-2-yl)benzo[d]thiazol-2-yl)urea (**5**):* To a solution of **iii** (165 mg, 0.626 mmol) in 1,4-dioxane (12 mL) was added **ii** (193 mg, 0.417 mmol) and $PdCl_2$(dppf) (34 mg, 0.042 mmol). A solution of Cs_2CO_3 (410 mg, 1.30 mmol) in H_2O (3 mL) was added, the reaction vessel sealed, then evacuated/purged with argon (x3). The mixture was then heated under microwave irradiation at 100 °C for 30 min. LCMS analysis indicated complete conversion. The mixture was diluted with EtOAc (100 mL), washed with H_2O, brine, then separated and dried (Na_2SO_4). The organic fraction was concentrated in vacuo. Purification by chromatography on silica, eluting with 0-10% MeOH/EtOAc followed by additional chromatography on silica, eluting with 0-10% MeOH/DCM afforded Compound **5** (9 mg, 5%).

Example(s) of General Method B

1-Ethyl-3-[5-[5-(1-hydroxyethyl)pyrazin-2-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea (**6**)



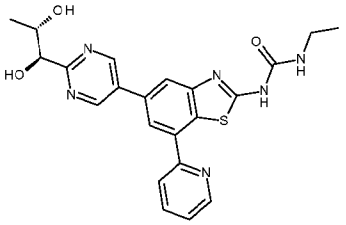
^{1}H NMR (400 MHz; d_6-DMSO): δ = 10.70 (bs, 1H), 9.43 (d, *J* = 1.5 Hz, 1H), 8.96 -8.78 (m, 2H), 8.71 (d, *J* = 1.5 Hz, 1H), 8.47 (t, *J* = 5.3 Hz, 2H), 8.14 -7.94 (m, 1H), 7.49 (ddd, *J* = 7.5, 4.9, 0.9 Hz, 1H), 6.88 (bt, *J* = 5.4 Hz, 1H), 5.65 (d, *J* = 4.7 Hz, 1H), 5.00 -4.84 (m, 1H), 3.29 -3.15 (m, 2H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H). MS: 421.08 $[M+H]^+$.

*1-[5-(5-acetylpyrazin-2-yl)-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (**i**):* **Intermediate 1** (171 mg, 0.5 mmol), 1-(5-chloropyrazin-2-yl)ethanone (94 mg, 0.60 mmol) and $PdCl_2$(dppf) (41 mg, 0.05 mmol) were suspended in 1,4-dioxane (8 mL). A solution of Cs_2CO_3 (488 mg, 1.50 mmol) in H_2O (2 mL) was added. The mixture was then heated under microwave irradiation at 100 °C for 30 min. The mixture was filtered, washed with H_2O, EtOH, MeOH and Et_2O to afford **i** (172 mg, 82%). MS: 419.06 $[M+H]^+$.

*1-ethyl-3-(5-(5-(1-hydroxyethyl)pyrazin-2-yl)-7-(pyridin-2-yl)benzo[d]thiazol-2-yl)urea (**6**):* To a suspension of **i** (63 mg, 0.15 mmol) in THF (5 mL) was added a solution of $NaBH_4$ (29 mg, 0.75 mmol) in H_2O (1 mL) and the mixture stirred at RT for 30 min. The reaction was diluted with EtOAc (50 mL) and washed with H_2O and brine. The organic fraction was dried (Na_2SO_4) and concentrated in vacuo to afford Compound **6** (62 mg, 98%).

Example(s) of General Method C

1-[5-[2-[(1S*,2R*)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (**7**)



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 2H), 8.70 (s, 1H), 8.14 - 7.90 (m, 2H), 7.82 (t, J = 7.3 Hz, 1H), 7.75 (s, 1H), 7.30 (d, J = 10.5 Hz, 1H), 4.55 (s, 1H), 4.14 (d, J = 7.2 Hz, 1H), 3.23 (s, 2H), 1.42 (d, J = 3.9 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H). MS: 451.1 $[M+H]^+$.

*(5-bromopyrimidin-2-yl)methanol (**i**):* An solution of $NaBH_4$ (510 mg, 2.70 mmol) in H_2O (10 mL) was introduced drop-wise to a solution of methyl 5-bromopyrimidine-2-carboxylate (3.05 g, 14.1 mmol) in THF (100 mL) at 0 °C. The mixture was allowed to warm slowly to RT overnight. The majority of the THF was evaporated, and the resulting residue was diluted with EtOAc (200 mL). The organic fraction was washed

with brine (200 mL), dried ($MgSO_4$) and purified over silica, eluting with 0-60% EtOAc:*n*-heptane) to afford **i** (510 mg, 19%). MS: 189.0 & 191.0; 1:1 $[M+H]^+$.

*5-bromo-2-(bromomethyl)pyrimidine (**ii**):* Methanesulfonyl chloride (0.31 mL, 4.0 mmol) was added to a stirred suspension of **i** (510 mg, 2.7 mmol) and triethylamine (820 µL, 5.9 mmol) in THF (30 mL) at 0°C for 10 min. The solution was treated with LiBr (1.2 g, 13 mmol) in THF (25 mL) and allowed to stir, whilst warming to RT over 1 h. The majority of the reaction solvent was removed *in vacuo*, and the mixture diluted with EtOAc (200 mL). The organic fraction was sequentially washed with sat. aq. NH_4Cl (2 x 100 mL), brine (1 x 100 mL) and dried ($MgSO_4$) to afford **ii** (663 mg, 98%). MS: 251.0, 253.0 & 254.8; 1:2:1 $[M+H]^+$.

*5-bromo-2-(diethoxyphosphorylmethyl)pyrimidine (**iii**):* Compound **ii** (663 mg, 2.63 mmol) was dissolved in 10 mL of ACN and triethylphosphite (0.92 mL, 5.26 mmol) added. The reaction was heated in a microwave for 1h at 100 °C. The reaction was concentrated *in vacuo* affording **iii** (813 mg, 100%) MS: 308.9 & 310.9; 1:1 $[M+H]^+$.

*1-[5-[2-(diethoxyphosphorylmethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (**iv**):* **Intermediate 1** (860 mg, 2.5 mmol), **iii** (813 mg, 2.63 mmol), Cs_2CO_3 (2.57 g, 7.90 mmol) and $Pd(PPh_3)_2Cl_2$ (90 mg, 0.10 mmol) were dissolved in 1-4-dioxane: H_2O (10:1; 10 mL) and degassed with a stream of N_2 for 10 min. The reaction was sealed under an atmosphere of N_2 and heated at 100 °C for 1 h in a microwave reactor. The mixture was concentrated *in vacuo*, purified over silica (gradient elution: 0-10% DCM-MeOH) and triturated from acetone affording **iv** (410 mg, 29%).MS: 527.1 $[M+H]^+$.

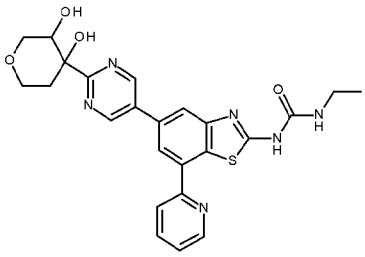
*1-ethyl-3-[5-[2-[(E)-prop-1-enyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea (**v**):* Sodium methoxide (0.5 M MeOH solution; 0.9 mL, 0.43 mmol) was added drop-wise to a suspension of **iv** (104 mg, 0.198 mmol) in THF (10 mL). Acetaldehyde (40 µL, 0.69 mmol) was introduced and the mixture stirred for 90 min. The reaction was diluted with EtOAc (60 mL), washed with sat. $NaHCO_3$(aq) (60 mL). The organic fraction was dried ($MgSO_4$), concentrated *in vacuo*, and purified over silica (gradient elution: 0-10%, DCM-MeOH) affording **v** (79 mg, 96%). MS: 417.1 $[M+H]^+$.

1-[5-[2-[(1S,2R*)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (**7**):* Osmium tetroxide (10 mg; 60 µmol) was added to a solution of **v** (230 mg, 600 µmol), *N*-methylmorpholine *N*-oxide (160 mg; 1.40 mmol) and pyridine (20µL) in THF-Me_2CO (5:1; 90 mL). The reaction was quenched

with sat. $Na_2S_2O_5$(aq) (20 mL), extracted with EtOAc (150 mL), washed with brine (75 mL). dried ($MgSO_4$) and concentrated *in vacuo.* Purification over silica (gradient elution: 0-10%, DCM-MeOH) afforded Compound **7** (93 mg, 38%).

Example(s) of General Method D

1-(5-(2-(3,4-dihydroxytetrahydro-2H-pyran-4-yl)pyrimidin-5-yl)-7-(pyridin-2-yl)benzo[d]thiazol-2-yl)-3-ethylurea (**8**)



^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 9.34 (s, 2H), 8.83 (dd, J = 4.8, 0.8 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.4 Hz, 1H), 8.15 (d, J = 0.9 Hz, 1H), 8.02 (td, J = 7.9, 1.8 Hz, 1H), 7.53 - 7.41 (m, 1H), 6.94 - 6.77 (m, 1H), 5.41 (s, 1H), 4.76 (t, J = 7.5 Hz, 1H), 3.93 (d, J = 11.0 Hz, 2H), 3.82 - 3.70 (m, 2H), 3.69 - 3.62 (m, 1H), 3.28 - 3.15 (m, 2H), 2.69 - 2.55 (m, 1H), 1.81 (d, J = 13.8 Hz, 1H), 1.12 (t, J = 7.2 Hz, 3H).MS: 493.1, $[M+H]^+$.

*5-bromo-2-(3,6-dihydro-2H-pyran-4-yl)pyrimidine (**i**):* 5-bromo-2-iodo-pyrimidine (250 mg; 0.88 mmol) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (196 mg, 0.92 mmol) were dissolved in 1,4-dioxane- H_2O (10: 1; 10 mL) and degassed with a stream of N_2 for 10 min. $Pd(Ph_3)_2Cl_2$ (30 mg, 0.04 mmol) was introduced and the reaction sealed and heated in a microwave reactor for 30 min at 80°C. The reaction was concentrated *in vacuo*, re-dissolved in DCM, filtered and purified over silica (gradient elution, 0-50% EtOAc-*n*-heptane) yielding **i** (105 mg, 50%). MS: 241.1 & 243.0; 1:1 $[M+H]^+$.

*5-bromo-2-(3,7-dioxabicyclo[4.1.0]heptan-6-yl)pyrimidine (**ii**):* Compound **i** (105 mg; 0.436 mmol) was dissolved in DCM (15 mL) and cooled to 0 °C, then solid 3-chlorobenzenecarboperoxoic acid (280 mg, 1.14 mmol) was added and the mixture stirred overnight. The mixture was quenched with 1M $Na_2S_2O_3$(aq) (5 mL), washed with sat. $NaHCO_3$(aq) (3 x 30 mL) followed by brine (1 x 30 mL). The organic fraction was dried ($MgSO_4$). Purification by chromatography on silica eluting with 0-50% EtOAc-*n*-heptane gave **ii** (20 mg, 18%). MS: 256.9 & 258.8; 1:1 $[M+H]^+$.

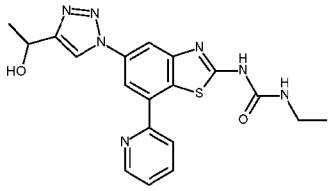
*1-[5-[2-(3,7-dioxabicyclo[4.1.0]heptan-6-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (**iii**):* **Intermediate 1** (29 mg, 0.085 mmol), **ii** (20 mg, 78 μmol), Cs_2CO_3 (55 mg 0.17 mmol) and $Pd(Ph_3)_2Cl_2$ (3 mg, 4 μmol) were dissolved in 1,4-dioxane: H_2O (10:1, 10 mL). The mixture was degassed with a stream of N_2 for 10 min, then heated in a microwave reactor at 80°C for 1 h.The reaction was concentrated *in vacuo*, re-dissolved in a minimum quantity of DCM and purified by

chromatography on silica (0-10% DCM-MeOH) yielding **iii** (23 mg 57%). MS: 475.0, $[M+H]^+$.

*1-(5-(2-(3,4-dihydroxytetrahydro-2H-pyran-4-yl)pyrimidin-5-yl)-7-(pyridin-2-yl)benzo[d]thiazol-2-yl)-3-ethylurea (**8**):* Compound **iii** (20 mg; 0.042 mmol) was dissolved in THF- H_2O (10:1, 11 mL). Conc. sulfuric acid (20 µL) and *p*-toluenesulphonic acid (0.7 mg, 4 µmol) were added and the mixture stirred at RT. The mixture was concentrated *in vacuo* and purified over silica (0-100% 0.1% FA(aq) - MeCN) yielding Compound **8** (8.8 mg, 42%).

Example(s) of General Method E

1-Ethyl-3-[5-[4-(1-hydroxyethyl)triazol-1-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea (**9**)



^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (br s, 1H), 8.91 (s, 1H), 8.84 (d, *J* = 3.9 Hz, 1H), 8.46 (d, *J* = 8.2 Hz, 1H), 8.41 (s, 1H), 8.16 (s, 1H), 8.03 (td, *J* = 7.9, 1.8 Hz, 1H), 7.49 (dd, *J* = 7.2, 5.2 Hz, 1H), 7.02 (br s, 1H), 5.41 (d, *J* = 4.8 Hz, 1H), 5.00 - 4.92 (m, 1H), 3.26 - 3.15 (m, 2H), 1.52 (d, *J* = 6.5 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H). MS: 410.0 $[M+H]^+$.

1-(5-azido-7-bromo-1,3-benzothiazol-2-yl)-3-ethylurea (i): **Intermediate 3** (3.0 g, 7.04 mmol), sodium azide (930 mg, 14.08 mmol), sodium L-ascorbic acid (350 mg, 1.8 mmol) and CuI (120 mg; 0.63 mmol) were suspended in a mixture of DMSO (100 mL) and H_2O (24 mL). *N,N'*-dimethylethane-1,2-diamine (100 mg, 1.1 mmol) was added and the suspension heated at 100°C overnight. H_2O was added and the resultant solid collected by filtration. This was rinsed with H_2O and dried *in vacuo* to give **i** (1.68 g). MS: 342.9 $[M+H]^+$.

1-{7-bromo-5-[4-(diethoxymethyl)-1H-1,2,3-triazol-1-yl]-1,3-benzothiazol-2-yl}-3-ethyl-5-methyl-1,3,5-triazinan-2-one (ii): Compound **i** (1.68 g, 4.89 mmol) was suspended in MeOH (65 mL) and formaldehyde (37wt% in H_2O, 7.94 g, 97.9 mmol) then methylamine (2 M in MeOH; 24.5 mL, 49 mmol) added. The suspension was heated to 80 °C for 5 h. H_2O was added and the mixture extracted with EtOAc and then DCM. The organic layers were dried (Na_2SO_4), filtrated and concentrated *in vacuo* to give a residue that contained 1-(5-azido-7-bromo-1,3-benzothiazol-2-yl)-3-ethyl-5-methyl-1,3,5-triazinan-2-one (1.31 g). A part of this mixture (827 mg; 2.09 mmol) was suspended in DMF (36 mL), cooled down at 0°C and then treated with 3,3-diethoxyprop-1-yne (535 mg, 4.17 mmol), DIPEA (320 mg, 2.5 mmol) and CuI (70 mg; 0.37 mmol). The ice bath was removed and the reaction let to stir overnight at

RT. The mixture was freeze-dried and the residue purified by chromatography on silica (0-5% MeOH gradient in DCM) to give a residue that was triturated with EtOAc affording **ii** (354 mg, 13%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.26 (d, *J* = 1.8 Hz, 1H), 8.10 (d, *J* = 1.8 Hz, 1H), 5.75 (s, 1H), 5.13 (s, 2H), 4.40 (s, 2H), 3.63 (qq, *J* = 9.6, 7.1 Hz, 4H), 3.38 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 6H), 1.13 (t, *J* = 7.1 Hz, 3H).

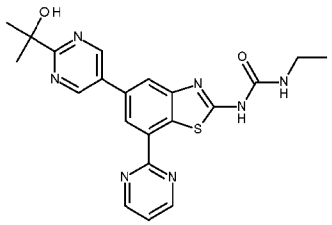
*1-{5-[4-(diethoxymethyl)-1H-1,2,3-triazol-1-yl]-7-(pyridin-2-yl)-1,3-benzothiazol-2-yl}-3-ethyl-5-methyl-1,3,5-triazinan-2-one (**iii**):* Compound **ii** (415 mg, 0.79 mmol) was suspended in DMF (5 mL) and tributyl(2-pyridyl)stannane (250 mg, 1.68 mmol) added. The mixture was degassed by freeze-drying the reaction vessel under *vacuo* and back filling with argon. CuI (30 mg, 0.2 mmol) and $Pd(PPh_3)_2Cl_2$ (1:2) (60 mg, 0.08 mmol) were added. The mixture was degassed with argon and heated at 110°C overnight. The mixture was filtered through celite, washing with DMF. The filtrate was freeze-dried to give a residue that was purified by chromatography on silica (0-100% EtOAc gradient in heptane) to give **iii** (250 mg, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (br s, 1H), 8.85 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H), 8.52 - 8.49 (m, 1H), 8.30 (d, *J* = 2.0 Hz, 1H), 8.06 - 8.01 (m, 1H), 7.49 (ddd, *J* = 7.5, 4.9, 0.9 Hz, 1H), 5.79 (s, 1H), 5.16 (s, 2H), 4.39 (s, 2H), 3.72 - 3.59 (m, 4H), 3.40 (q, *J* = 7.1 Hz, 2H), 2.56 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 6H), 1.14 (t, *J* = 7.1 Hz, 3H). MS: 523.0 $[M+H]^+$.

*1-Ethyl-3-[5-(4-formyl-1H-1,2,3-triazol-1-yl)-7-(pyridin-2-yl)-1,3-benzothiazol-2-yl]urea (**iv**):* Compound **iii** (250 mg, 0.48 mmol) was suspended in 1M HCl solution (9 mL) and the mixture heated at 70°C overnight. The mixture was concentrated *in vacuo* to give **iv** (213 mg, quantitative). MS: 394.0 $[M+H]^+$.

*1-ethyl-3-{5-[4-(1-hydroxyethyl)-1H-1,2,3-triazol-1-yl]-7-(pyridin-2-yl)-1,3-benzothiazol-2-yl}urea (**9**):* To a suspension of **iv** (40 mg, 0.1 mmol) in THF (0.7 mL) was added bromo(methyl)magnesium 3M in Et_2O (0.250 mL, 0.1 mmol) and the mixture heated at 40°C for 1 h. NH_4Cl (sat. aq.) was added and the mixture extracted with DCM :IPA (5:1). The organic layers were washed with brine and then concentrated *in vacuo* to give a crude product that was purified by reverse phase SP4 (ACN gradient in H_2O) affording Compound **9** (1.9 mg, 4%).

Example(s) of General Method F

1-Ethyl-3-(5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7-(pyrimidin-2-yl)benzo[d]thiazol-2-yl)urea (**10**)

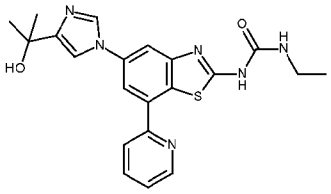


^{1}H NMR (DMSO-d_6): δ□10.72 (br s, 1H), 9.24 (s, 2H), 9.08 (d, *J*= 4.80 Hz, 2H), 8.70 (s, 1H), 8.23 (s, 1H), 7.57 (t, *J*= 4.80 Hz, 1H), 6.82 (m, 1H), 5.17 (s, 1H), 3.22 (m, 2H), 1.56 (s, 6H) and 1.12 (t, *J*= 7.20 Hz, 3H). MS: 436.15 $[M+H]^+$.

A solution of **Intermediate 5** (0.30 g, 0.68 mmol) and 2-(tributylstannyl)pyrimidine (0.253 g, 0.68 mmol) in DMF (10 mL) was degassed by purging with N_2 for 15 min followed by addition of $Pd(PPh_3)_4$ (0.078 g, 0.06 mmol). The mixture was degassed by purging with N_2 for 10 min and then heated to 80°C for 16 h. Ice-cold H_2O was added to the reaction followed by extraction with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified over silica (2.50% MeOH-DCM) to give Compound **10** (0.015 g, 5%).

Example(s) of General Method G

1-ethyl-3-(5-(4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-7-(pyridin-2-yl)benzo[d]thiazol-2-yl)urea (**11**)



^{1}H NMR (400 MHz, MeOD) δ 8.73 (d, J = 4.8 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.20 (d, J = 1.4 Hz, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.92 (td, J = 7.9, 1.8 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.55 (d, J = 1.4 Hz, 1H), 7.37 (dd, J = 7.5, 4.9 Hz, 1H), 3.37 - 3.32 (m, 2H), 1.62 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H). MS: 422.99 $[M+H]^+$.

*2-(1H-imidazol-4-yl)propan-2-ol (**i**):* Methyl 1H-imidazole-4-carboxylate (430 mg) was heated at reflux in HMDS (1 mL) for 30 min and the excess HMDS then distilled off. The residue was placed under vacuum then flushed twice with N_2 before dissolving in THF. The solution was cooled to 0°C, and MeMgBr (4.5 mL ; 3M) added dropwise at 0°C and the mixture warmed to RT overnight. The mixture was quenched with 1mL sat. NH_4Cl then diluted with 2-3mL H_2O. The mixture was concentrated *in vacuo* to an aqueous emulsion which was applied to a 12g C18 reverse phase column. Elution with 100% ACN gave a residue that was further purified by chromatography on silica eluting with MeOH/DCM to afford **i** (280 mg).

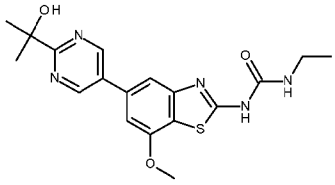
*1-ethyl-3-(5-(4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-7-(pyridin-2-yl)benzo[d]thiazol-2-yl)urea (**11**) :* Compound **i** (74 mg) and **Intermediate 1** (100 mg) were suspended in pyridine with 4Å mol. sieves. The mixture was degassed and flushed with oxygen and $Cu(OAc)_2.H_2O$ added. The mixture was again degassed and

flushed with oxygen then left stirring at 80°C for 280 min. The reaction was quenched by adding NH_4Cl sat. and diluted with EtOAc and H_2O. The mixture was extracted with EtOAc and the organics combined, dried (Na_2SO_4) and evaporated to dryness. Purification by chromatography on silica, eluting with DCM/MeOH (0-10%) followed by reverse phase chromatography on a C18 column eluting with ACN/H_2O afforded Compound **11** (7.5 mg).

Example(s) of Further Functionalisation

Alkylation of a hydroxyl group

1-Ethyl-3-(5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7-methoxybenzo[d]thiazol-2-yl)urea (**12**)

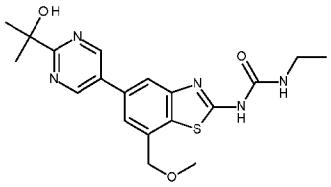


^{1}H NMR (400 MHz, Acetone-d_6) δ 9.22 (d, J = 2.7 Hz, 2H), 7.65 (s, 1H), 7.22 (s, 1H), 4.11 (s, 3H), 3.44 - 3.26 (m, 2H), 1.60 (s, 6H), 1.19 (t, J = 7.2 Hz, 3H). MS: 388.03 $[M+H]^+$.

A solution of **Intermediate 9** (240 mg) and Cs_2CO_3 (220mg) in anhydrous DMF (10mL) was chilled to 0°C then treated with iodomethane (83.5mg). The reaction was allowed to warm to RT over 90 min then quenched with H_2O. The mixture was concentrated under vacuum and the resulting residue suspended in DCM & minimal MeOH for purification by chromatography on silica (0 - 5% MeOH:DCM). The residue was suspended in THF (10mL) and treated with 1M HCl (10mL). The reaction was stirred at RT for 90 min then neutralised with $NaHCO_3$ solution. The mixture was diluted with EtOAc (15mL) and a white solid formed between the aqueous and organic layers. The solid was collected by filtration and dried under vacuum with heating at 50°C to give Compound **12** (83mg).

Ether formation from a halo moiety via an aldehyde

1-Ethyl-3-(5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7-(methoxymethyl)benzo[d]thiazol-2-yl)urea (**13**)



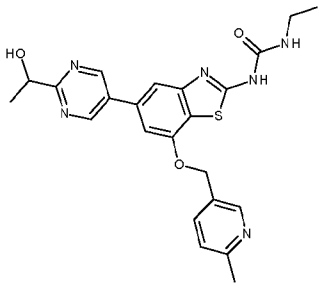
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 2H), 7.95 (s, 1H), 7.23 (s, 1H), 4.67 (s, 2H), 3.48 (dd, *J* = 12.1, 6.3 Hz, 2H), 3.44 (s, 3H), 1.63 (s, 6H), 1.33 - 1.21 (m, 3H). MS 402.04 $[M+H]^+$.

2-(3-ethyl-5-methyl-2-oxo-1,3,5-triazinan-1-yl)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazole-7-carbaldehyde (i): A solution of

Intermediate 4 (200mg, 0.41mmol) in THF (10mL) was chilled to -80°C under N_2 then treated with nBuLi (0.89mL, 1.22mmol). After 1 min DMF (0.06mL, 0.81mmol) was added and the reaction allowed to warm to RT over 30 min. The reaction was diluted with $NaHCO_3$ (20mL) then extracted with EtOAc (2 x 15mL). The organic extract was dried ($MgSO_4$), filtered and concentrated. The residue was suspended in DCM then purified by chromatography on silica eluting with (0 - 5% MeOH :DCM) to give **i** (38.5mg, 22%). MS 441.01 $[M+H]^+$.

1-Ethyl-3-(5-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7-(methoxymethyl)benzo[d] thiazol-2-yl)urea : A solution of **i** (23mg, 0.05mmol) in MeOH (2mL) was treated with H_2SO_4 (20mL, 0.38mmol) then stirred at RT for 90 min. The reaction was neutralised with $NaHCO_3$, then extracted with EtOAc (2 x 10mL). The organic extract was dried ($MgSO_4$), filtered and concentrated. The crude material was suspended in DCM (2mL) and treated with triethylsilane (50µL, 0.31mmol) and BF_3OEt_2 (25µL, 0.20mmol). The reaction was stirred at RT for 30 min, quenched with MeOH (2mL) and stirred for 1h. The mixture was diluted with EtOAc (5mL) and washed with $NaHCO_3$ (5mL) and H_2O (5mL). The organic extract was dried ($MgSO_4$), filtered and concentrated. The material was suspended in MeCN:MeOH and purified by reverse phase chromatography (5-40-50-100% MeCN:H_2O + 0.1% FA) to give Compound **13** (7.3mg, 21%).

1-ethyl-3-(5-(2-(1-hydroxyethyl)pyrimidin-5-yl)-7-((6-methylpyridin-3-yl)methoxy)benzo[d]thiazol-2-yl)urea (**14**)



^{1}H NMR (400 MHz, D_2O) δ 8.60 (s, 2H), 8.29 (s, 1H), 8.15 (d, J = 7.0 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 6.91 (s, 1H), 6.38 (s, 1H), 3.03 - 2.90 (m, 2H), 2.75 (s, 3H), 1.45 (t, J = 10.7 Hz, 3H), 1.00 (dt, J = 14.1, 7.1 Hz, 3H). MS: 465.1 $[M+H]^+$.

*1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[(6-methyl-3-pyridyl)methoxy]-1,3-benzothiazol-2-yl]-5-methyl-1,3,5-triazinan-2-one (**i**):* Methanesulfonyl chloride; (120 µL; 1.50 mmol) was introduced drop-wise to a solution of (6-methyl-3-pyridyl)methanol (100 mg; 0.812 mmol) and triethylamine (0.32 mL; 2.25 mmol) in anhydrous DCM (6 mL) at 0°C and stirring was continued for 30 min at 0 °C. The mixture was quenched with MeOH (2 mL), concentrated *in vacuo* and purified on

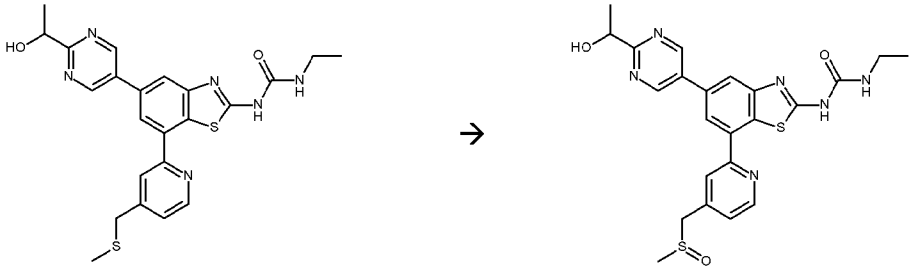
silica (gradient elution, 50-100%, *n*-heptane-EtOAc) affording 6-methyl-3-pyridyl)methyl methanesulfonate (95 mg, 58%).

In a separate flask, **Intermediate 10** (45 mg, 0.11 mmol) and K_2CO_3 (68 mg, 0.49 mmol) were dissolved in DMF (10 mL), and solution of (6-methyl-3-pyridyl)methyl methanesulfonate (95 mg, 0.47 mmol) in DMF (3 mL) was added at RT. The reaction was heated to 45°C for 3 h. Concentrating the reaction mixture to 1/3rd of its original volume and diluting with EtOAc (100 mL), washing with H_2O (100 mL), followed by brine (100 mL), and back extracting the aqueous phase with DCM:IPA (5:1, 100 mL) followed by purification by chromatography on silica eluting with 0-10%, DCM in MeOH gave **i** (30 mg, 53%).

*1-ethyl-3-(5-(2-(1-hydroxyethyl)pyrimidin-5-yl)-7-((6-methylpyridin-3-yl)methoxy)benzo[d]thiazol-2-yl)urea (**14**):* Compound **i** (30 mg; 58 µmol) was suspended in THF (3 mL) and concentrated HCl (1 mL) was introduced and heated to 45°C for 1.5 h.The reaction was concentrated *in vacuo*, and purified by reverse phase chromatography, gradient elution, 25-80%, 0.1%FA(aq) in ACN) and lyophilized in the presence of 1M HCl (ca. 3 mL) to give Compound **14** (23 mg, 79%).

Sulfone formation from a thioether

1-Ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(methylsulfanylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea (**15**); and 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(methylsulfinylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea (**16**)

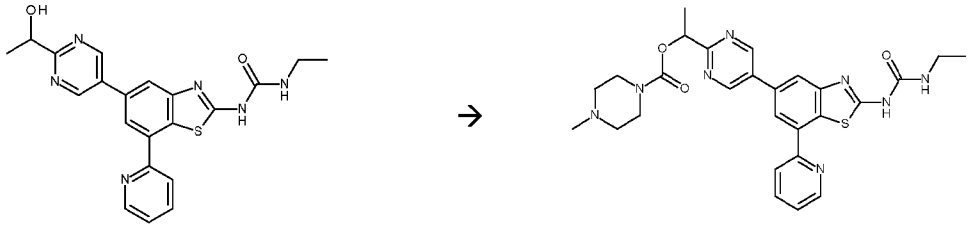


A solution of oxone (45 mg, 0.073 mmol) in H_2O (0.5 mL) was added to a solution of Compound **15** (70 mg, 0.146 mmol) in DMF (4.5 mL) at RT and stirred for 1 h.. The mixture was diluted with EtOAc (50 mL) and washed with H_2O. The aqueous fraction was saturated with NaCl and re-extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography on silica, eluting with 0-30% MeOH/EtOAc to afford Compound **16** (15 mg, 21%). MS: 496.97 $[M+H]^+$; ^1H NMR (400 MHz; d_6-DMSO): δ

= 10.79 (bs, 1H), 9.36 (s, 2H), 8.87 (d, *J* = 4.9 Hz, 1H), 8.52 (s, 1H), 8.39 (d, *J* = 1.5 Hz, 1H), 8.20 (d, *J* = 1.5 Hz, 1H), 7.47 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.03 (bd, *J* = 5.2 Hz, 1H), 5.35 (d, *J* = 5.5 Hz, 1H), 4.94 (p, *J* = 6.5 Hz, 1H), 4.36 (d, *J* = 12.5 Hz, 1H), 4.25 -4.07 (m, 1H), 3.28 (dd, *J* = 7.1, 5.7 Hz, 2H), 2.64 (s, 3H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H).

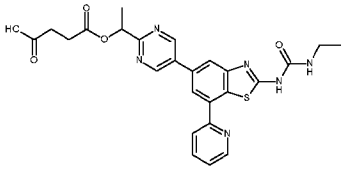
Example(s) of General Method H

1-Ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea (**17**); and 1-(5-(2-(3-ethylureido)-7-(pyridin-2-yl)benzo[d]thiazol-5-yl)pyrimidin-2-yl)ethyl 4-methylpiperazine-1-carboxylate (**18**)



Compound **17**, similarly prepared to Compound **1**, (0.2378 mmol; 100 mg) was dissolved in DMF (1 mL) and di(imidazol-1-yl)methanone (0.26 mmol; 42 mg) added and stirred at RT for 18 h. 1-Methylpiperazine (0.29 mmol; 29 mg) was added and the mixture stirred at RT for 18 h. The mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica eluting with 0-12% MeOH/ DCM) followed by reverse phase chromatography to give Compound **18** (12 mg) as the formate salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 9.39 (s, 2H), 8.84 (d, J = 4.0 Hz, 1H), 8.55 (d, J = 8.2 Hz, 1H), 8.42 (d, J = 1.4 Hz, 1H), 8.18 (d, J = 1.1 Hz, 1H), 8.03 (td, J = 7.9, 1.7 Hz, 1H), 7.48 (dd, J = 7.1, 5.1 Hz, 1H), 6.92 (t, J = 5.2 Hz, 1H), 4.54 (d, J = 12.9 Hz, 1H), 4.36 (d, J = 12.9 Hz, 1H), 3.27 - 3.18 (m, 2H), 2.77 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H). MS 453.01 [M+H]$^+$.

4-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethoxy]-4-oxo-butanoic acid (**19**)

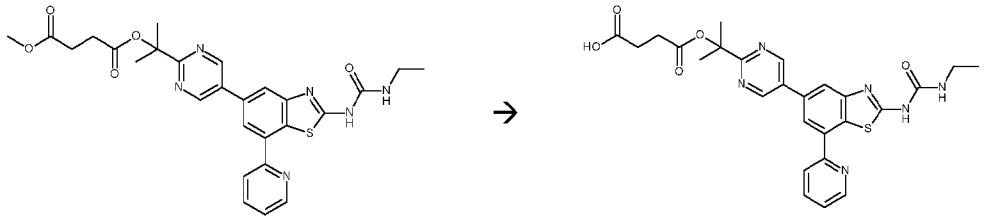


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 2H), 8.70 - 8.63 (m, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.83 - 7.67 (m, 3H), 7.20 - 7.13 (m, 1H), 5.83 (q, J = 6.8 Hz, 1H), 3.30 - 3.13 (m, 2H), 2.63 (dd, J = 6.8, 2.1 Hz, 2H), 2.52 (dd, J = 6.5, 2.9 Hz, 2H), 1.57 (d, J = 6.8 Hz, 3H), 1.09 (t, J = 7.3 Hz, 2H). MS 521.09 [M+H]$^+$.

A solution of Compound **17** (250 mg) was treated with DIPEA (230 mg), DMAP (40 mg) and succinic anhydride (150 mg) then stirred at 50°C for 6 h. Then DIPEA

(300μL) and succinic anhydride (100mg) were added and the reaction stirred overnight. The mixture was diluted with H_2O (30mL) and washed with EtOAc (3 x 15mL). The aqueous extract was concentrated to give a crude brown gum. Purification by chromatography on silica eluting with 0-5% MeOH in DCM gave a solid that was suspended in hot MeOH, left to cool to RT and the resulting solid collected by filtration and dried under vacuum to give Compound **19**.

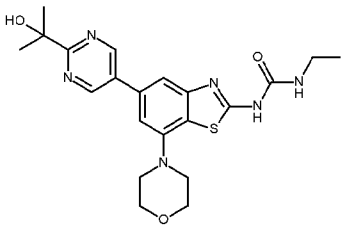
O4-[1-[5-[2-(Ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] O1-methyl butanedioate (**20**); and 4-((2-(5-(2-(3-ethylureido)-7-(pyridin-2-yl)benzo[d]thiazol-5-yl)pyrimidin-2-yl)propan-2-yl)oxy)-4-oxobutanoic acid (**21**)



Compound **20**, similarly prepared to Compound **1**, (179 mg, 0.33 mmol) was dissolved in MeOH (18 mL) and NaOH (0.65 mL, 1 M, aq) added. The solution was stirred at RT, then further NaOH (0.65 mL, 1 M, aq) was added after 1.5 h and 3.5 h. H_2O (0.5 mL) was added after 7 h. The solution was stirred at RT overnight. After 23 h, the mixture was acidified to pH 4.5 with HCl (1 M, aq) and the solution concentrated to dryness in vacuo, azeotroping with ACN (3 x 20 mL). The solid was purified by chromatography on silica, eluting with 0-5% MeOH in DCM, followed by further chromatography on silica eluting with 0-50% MeOH in EtOAc and further chromatography on silica eluting with 0-5% MeOH in DCM to give Compound **21** (47 mg, 27%). ^{1}H NMR (400 MHz, MeOD): δ 9.14 (s, 2H), 8.77 (ddd, J = 4.3, 1.7, 0.8 Hz, 1H), 8.29 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 1.5 Hz, 1H), 7.99 (d, J = 1.5 Hz, 1H), 7.96 (dt, J = 7.8 and 1.7 Hz, 1H), 7.40 (ddd, J = 7.4, 4.3, 0.8 Hz, 1H), 3.37 (q, J = 7.2 Hz, 2H), 2.71 (m, 2H), 2.60 (m, 2H), 1.87 (s, 6H), 1.27 (t, J = 7.2 Hz, 3H). MS: 535.05 $[M+H]^+$.

Example(s) of General Method I

1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-morpholino-1,3-benzothiazol-2-yl]urea (**151**)



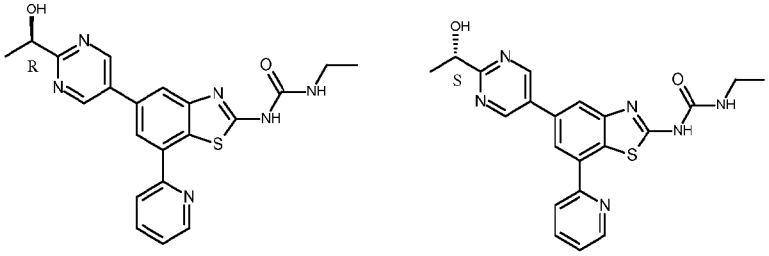
^{1}H NMR (400 MHz; DMSO-d_6): δ 10.75 (br s, 1H), 9.16 (s, 2H), 7.72 (s, 1H), 7.16 (s, 1H), 6.73 (m, 1H), 5.11 (s, 1H), 3.86 (m, 4H), 3.17-3.26 (m, 6H), 1.54 (s, 6H) and 1.09 (t, J= 7.20 Hz, 3H). MS: 443.28 $[M+H]^+$

*1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-morpholino-1,3-benzothiazol-2-yl]-5-methyl-1,3,5-triazinan-2-one (**i**):*To a solution of **Intermediate 4** (0.25 g, 0.51 mmol) in 1,4-dioxane (10 mL) was added morpholine (0.066 g, 0.77 mmol) followed by Cs_2CO_3 (0.25 g, 0.77 mmol). The resulting solution was purged with nitrogen for 30 min followed by addition of $Pd_2(dba)_3$ (0.026 g, 0.025 mmol) and Xantphos (0.035 g, 0.061 mmol). The reaction mixture was again purged with nitrogen for 15 min and then heated up to 80°C overnight. After the completion of reaction (TLC monitoring), the reaction was cooled to RT, filtered through celite bed, washed the celite bed with EtOAc and concentrated the combined filtrate under reduced pressure. The crude residue was then purified over silica gel (100-200 M, 3% MeOH-DCM) to obtain **i** as off-white solid (0.07 g, 28%). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 9.18 (s, 2H), 7.79 (s, 1H), 7.19 (s, 1H), 5.12 (s, 3H), 4.37 (s, 2H), 3.80-3.83 (m, 4H), 3.35-3.38 (m, 2H), 3.21-3.23 (m, 4H), 2.54 (s, 3H), 1.54 (s, 6H) and 1.08 (t, *J*= 6.80 Hz, 3H).

*1-Ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-morpholino-1,3-benzothiazol-2-yl]urea (**151**):* To an ice-cold solution of **i** (0.065 g, 0.13 mmol) in THF (3 mL) was added 6N-HCl (2 mL). The mixture was stirred at RT for 4 h. After completion of reaction (TLC monitoring), the mixture was poured into saturated $NaHCO_3$ solution followed by extraction with EtOAc (2 x 50 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was triturated with MeOH-Et_2O to affford Compound **151** as a white solid (0.035 g, 61%).

Example(s) of Chiral Separation and Synthesis

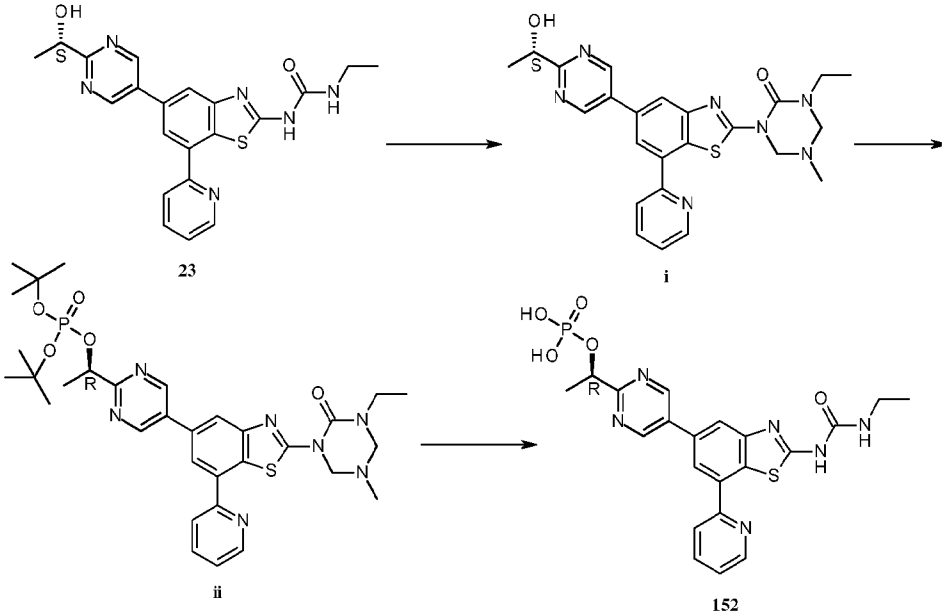
(R)-1-ethyl-3-(5-(2-(1-hydroxyethyl)pyrimidin-5-yl)-7-(pyridin-2-yl)benzo[d]thiazol-2-yl)urea (**22**) & (S)-1-ethyl-3-(5-(2-(1-hydroxyethyl)pyrimidin-5-yl)-7-(pyridin-2-yl)benzo[d]thiazol-2-yl)urea (**23**)



The (R) and (S) enantiomers of Compound **17** were separated by chiral prep-HPLC:

Column:	Chiralpak IC (250 x 20 mm) 5 μ
Mobile phase:	100% MeOH
Sampling details:	25mg in a mix of 0.5 mL TFA and 0.5mL of MeOH
Flow rate:	18 mL/min.
Run time:	20 min.
Retention Time	9.3 min; 14.7 min.

[(1R)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] dihydrogen phosphate (**152**); & [(1S)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] dihydrogen phosphate (**153**)



1-ethyl-3-[5-[2-[(1S)-1-hydroxyethyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-5-methyl-1,3,5-triazinan-2-one (i): Compound **23** (12.67 g, 30.13 mmol) was suspended in MeOH (150 mL). Formaldehyde (48.9 mL, 0.603 mol, as a 37% aqueous solution) was added, along with *N*-methylmorpholine (33.1 mL, 0.301 mol) and methylamine (151 mL of a 2M THF solution). The white suspension was heated at 70°C overnight. TLC showed almost complete conversion to product after 19hrs

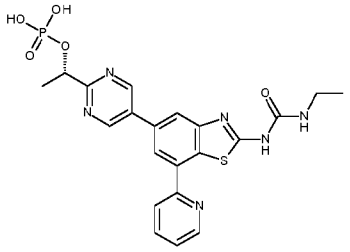
and the solution was cooled to room temperature then concentrated to ~33% volume under reduced pressure and partitioned between H_2O (150 mL) and EtOAc (300 mL). Heat was applied to the biphasic mixture to help solubilize the product. The organic layer was washed with brine, filtered through $MgSO_4$, and concentrated to dryness under reduced pressure. The solid was swished in EtOAc (100 mL), filtered, washed with EtOAc and heptane, and dried to give **i** as a white solid (11.97 g, 76%). MS: 475.93 $[M+H]^+$.

*Di-tert-butyl [(1R)-1-[5-[2-(3-ethyl-5-methyl-2-oxo-1,3,5-triazinan-1-yl)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] phosphate (**ii**)*:

Preparation of *di-tert-butyl hydrogen phosphate*: Potassium di-tert-butyl phosphate (45 g) was dissolved in water (160 mL). Hydrochloric acid (1 M, aq) was added until the pH was ~3. The resultant precipitate was collected by filtration, washed with water, and dried under vacuum overnight to give di-tert-butyl phosphonic acid as a white solid. Then, to a suspension of **i** (18.68 g, 39.28 mmol), triphenylphosphine (17.51 g, 66.78 mmol), and di-tert-butyl hydrogen phosphate (10.73 g, 51.06 mmol) in THF and triphenylphosphine were suspended in anhydrous THF (200 mL). A solution of DIAD (13.5 g, 66.78 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at room temperature and monitored by LCMS to completion then was concentrated under reduced pressure. Et_2O (300 mL) was added and the mixture sonicated, resulting in a bright white solid, which was filtered, washed with Et_2O (100 mL) and air dried. The filtrate also contained some product. After concentration to 150 mL the filtrate was chilled in ice, yielding more solid material. The solids were collected, redissolved in DCM, and plugged (50-100% EtOAc/DCM to remove Mitsonobu by-products then 10% MeOH/DCM to elute the desired product. After concentrating the relevant fraction to a white solid, this material was recrystallized from DCM/ether/heptane, filtered, washed with heptane, and dried overnight to give **ii** as a white solid (17.09 g, 64%). ^{1}H NMR (400 MHz) δ 9.41 (s, 2H); 8.83 (d, J = 4.4 Hz, 1H); 8.53 (d, J = 8 Hz, 1H); 8.43 (d, J = 1.2 Hz, 1H); 8.21 (d, J = 1.2 Hz, 1H); 8.01 (dt, J = 8, 1.6 Hz, 1H); 7.46 (dd, J = 7.2, 4.8 Hz); 5.43 (m, 1H); 5.16 (s, 2H); 4.38 (s, 2H); 3.39 (q, J = 7.2 Hz, 2H); 3.32 (br s, 2H); 2.55 (s, 3H); 1.64 (d, J = 6.8 Hz, 3H); 1.38 (s, 9H); 1.36 (s, 9H); 1.14 (t, J = 7.2 Hz). MS: 667.78 $(M+H)^+$. Chiral HPLC: Column: Chirapak IC, 0.46 cm x 25 cm; 25 min isocratic gradent 100% MeOH retention time = 17.12 min.

[(1R)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-

*2-yl]ethyl] dihydrogen phosphate (**152**)*: A solution of **ii** (17.0 g, 25.46 mmol) in anhydrous THF (300 mL) was treated with 4 M HCl in dioxane (63.6 mL, 10 eq.). A precipitate formed immediately upon addition of acid and the reaction monitored to completion by LCMS. H_2O (50 mL) was added and the solution concentrated to remove approx. 150 mL of THF, at which point a flocculent precipitate began to form. The mixture was stirred at room temperature overnight, yielding a white precipitate which was filtered, washed several times with water, followed by MeOH and Et_2O, then dried at 50°C for 6 hours to give Compound **152** as a white solid (12.0 g, 95%). MS: 501.7 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.7 (br s 1H), 9.35 (s, 2H), 8.85 – 8.81 (m, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.49 – 7.44 (m, 1H), 6.93 (t, J = 5.5 Hz, 1H), 5.48 – 5.39 (m, 1H), 3.27 – 3.17 (m, 2H), 1.63 (d, J = 6.6 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H). Compound **153** may be similarly prepared, starting from Compound **22**.



^1H NMR (400 MHz, DMSO-d_6): δ 10.6 (br s, 1H), 9.35 (s, 2H), 8.85 – 8.81 (m, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.56 – 7.31 (m, 1H), 6.89 (t, J = 5.5 Hz, 1H), 5.47 – 5.38 (m, 1H), 3.26 – 3.18 (m, 2H), 1.63 (d, J = 6.6 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H). MS: 501.05 $[M+H]^+$.

The following compounds were similarly prepared with reference to the general method(s) and/or examples previously described.

Table 1: *Compounds and characterisation data*

No.	Observed LCMS $[M+H]^+$	^1H NMR
24	486	(DMSO-d_6): δ 10.62 (s, 1H), 9.0 (s, 1H), 8.8 (d, 1H), 8.5 (d, 1H), 8.4 (d, 1H), 8.35 (s, 1H), 8.05 (m, 2H), 7.8 (s, 1H), 7.5 (m, 1H), 7.1 (s, 1H), 6.9 (s, 1H), 6.8 (s, 1H), 6.3 (d, 1H), 6.0 (d, 1H), 3.7 (s, 3H), 3.25 (m, 2H), 1.15 (t, 3H)
25	534.15	($CDCl_3$): δ 9.22 (s, 2H), 8.66 (s, 1H), 8.13 (s, 1H), 7.89 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.77 (s, 1H), 3.84 – 3.67 (m, 4H), 3.58 (s, 2H), 3.41 (s, 2H), 2.51 (s, 4H), 1.61 (s, 6H), 1.31 – 1.26 (m, 3H).
26	518.17	($CDCl_3$) δ 9.18 (s, 2H), 8.66 (d, J = 4.7 Hz, 1H), 8.46 (s, 1H), 8.16 (s, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 3.92 (s, 2H), 3.51 – 3.36 (m, 2H), 2.80 (s, 4H), 1.92 (s, 4H), 1.63 (s, 6H), 1.35 – 1.22 (m, 3H).

27	434.05	($CDCl_3$) δ 8.91 (d, J = 1.6 Hz, 1H), 8.59 (d, J = 4.5 Hz, 1H), 8.12 – 7.98 (m, 4H), 7.82 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.21 (dd, J = 7.2, 5.0 Hz, 1H), 3.56 – 3.43 (m, 2H), 1.59 (s, 6H), 1.32 (t, J = 7.2 Hz, 3H).
28	534.18	(DMSO-d_6) δ 10.63 (br s, 1H); 9.35 (s, 2H); 8.77 (d, J = 5 Hz, 1H); 8.44 (1H, s); 8.39 (1H, s); 8.15 (1H, s); 7.47 (d, J = 5 Hz, 1H); 6.90 (br s, 1H); 5.15 (s, 1H); 3.66 (s, 2H); 3.63 (s, 4H); 3.23 (m, 2H); 2.46 (s, 4H); 1.59 (s, 6H); 1.14 (t, J = 7 Hz, 3H). Methano sulphonate salt form: ^{1}H NMR (400 MHz; D_2O): δ = 8.70 (s, 2H), 8.25 (s, 1H), 7.83 (s, 1H), 7.34 (s, 1H), 7.17 (s, 2H), 4.28 (s, 2H), 4.00 (s, 4H), 3.33 (s, 4H), 3.21–3.02 (m, 2H), 2.83 (s, 3H), 1.66 (s, 6H), 1.12 (t, *J* = 7.2 Hz, 3H). MS: 534.19 $[M+H]^+$ HCl salt form: ^{1}H NMR (400 MHz; DMSO-d_6): δ = 12.24 (bs, 1H), 9.45 (s, 2H), 9.11 (s, 1H), 8.92 (d, *J* = 5.0 Hz, 1H), 8.55 (d, *J* = 1.5 Hz, 1H), 8.22 (d, *J* = 1.5 Hz, 1H), 7.66 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.20 (bs, 1H), 4.54 (s, 2H), 3.96 (s, 4H), 3.46–3.29 (m, 2H), 3.29–3.09 (m, 4H), 1.59 (s, 6H), 1.14 (t, *J* = 7.2 Hz, 3H). MS: 534.18 $[M+H]^+$
29	534.3	(DMSO-d_6) δ 10.80 (br s, 1H), 9.32 (s, 2H), 8.75 (d, J= 4.80 Hz, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.12 (s, 1H), 7.42 (d, J= 4.80 Hz, 1H), 7.05 (m, 1H), 5.16 (br s, 1H), 4.74 (br s, 1H), 4.22 (br s, 1H), 3.67-3.78 (m, 2H), 3.38 (m, 2H), 3.17-3.24 (m, 2H), 2.73-2.75 (m, 1H), 2.63-2.67 (m, 1H), 2.37-2.40 (m, 1H), 2.01-2.06 (m, 1H), 1.56 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).
30	520.25	(DMSO-d_6) δ 10.67 (br s, 1H), 9.33 (s, 2H), 8.73 (d, J= 4.80 Hz, 1H), 8.36 (br s, 2H), 8.12 (s, 1H), 7.35 (d, J= 4.80 Hz, 1H), 6.92 (m, 1H), 5.35 (d, J= 6.40 Hz, 1H), 5.15 (s, 1H), 4.21-4.26 (m, 1H), 3.71 (s, 2H), 3.58 (t, J= 6.40 Hz, 2H), 3.21 (m, 2H), 2.85 (t, J= 6.40 Hz, 2H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).
31	534.28	(DMSO-d_6) δ 10.62 (br s, 1H), 9.35 (s, 2H), 8.73 (d, J= 4.80 Hz, 1H), 8.38 (m, 2H), 8.13 (s, 1H), 7.35 (d, J= 4.80 Hz, 1H), 6.86 (m, 1H), 5.15 (s, 1H), 4.0-4.03 (m, 1H), 3.74 (s, 2H), 3.57 (t, J= 6.40 Hz, 2H), 3.21 (m, 2H), 3.15 (s, 3H), 2.93 (m, 2H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).
32	564.3	(DMSO-d_6) δ 10.62 (br s, 1H), 9.33 (s, 2H), 8.61 (d, J= 5.60 Hz, 1H), 8.40 (s, 1H), 8.12 (s, 1H), 8.03 (s, 1H), 7.05 (m, 1H), 6.90 (m, 1H), 5.15 (s, 1H), 4.34 (t, J= 5.60 Hz, 2H), 3.57-3.59 (m, 4H), 3.31-3.36 (m, 4H), 3.19-3.22 (m, 2H), 2.76 (t, J= 5.60 Hz, 2H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).
33	548.31	(DMSO-d_6) δ 10.61 (br s, 1H), 9.33 (s, 2H), 8.76 (d, J= 4.80 Hz, 1H), 8.39 (s, 2H), 8.13 (s, 1H), 7.42 (m, 1H), 6.85 (m, 1H), 5.15 (s, 1H), 3.53-3.58 (m, 5H), 3.18-3.25 (m, 2H), 2.50 (m, 2H), 2.32 (m, 2H), 1.57 (s, 6H), 1.38 (d, J= 6.80 Hz, 3H), and 1.11 (t, J= 7.20 Hz, 3H).

34	554.25	(DMSO-d_6) δ 10.63 (br s, 1H), 9.33 (s, 2H), 8.76 (d, J= 4.80 Hz, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 8.14 (s, 1H), 7.43 (m, 1H), 6.86 (m, 1H), 5.16 (s, 1H), 3.79 (s, 2H), 3.18-3.24 (m, 2H), 2.92-2.99 (m, 2H), 2.78 (t, J= 6.80 Hz, 2H), 2.23-2.34 (m, 2H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).
35	536.28	(DMSO-d_6) δ 10.63 (br s, 1H), 9.32 (s, 2H), 8.75 (d, J= 4.80 Hz, 1H), 8.50 (s, 1H), 8.38 (s, 1H), 8.13 (s, 1H), 7.42 (d, J= 4.80 Hz, 1H), 6.86 (t, J= 5.20 Hz, 1H), 5.15 (m, 2H), 3.78 (s, 2H), 3.18-3.33 (m, 2H), 2.80-2.89 (m, 2H), 2.66-2.68 (m, 1H), 2.39-2.50 (m, 1H), 2.12-2.19 (m, 1H), 1.89-1.98 (m, 1H), 1.56 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).
36	536.26	(DMSO-d_6) δ 10.62 (br s, 1H), 9.32 (s, 2H), 8.75 (d, J= 4.80 Hz, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 8.13 (s, 1H), 7.43 (d, J= 4.80 Hz, 1H), 6.86 (t, J= 5.20 Hz, 1H), 5.15 (m, 2H), 3.78 (s, 2H), 3.19-3.23 (m, 2H), 2.80-2.89 (m, 2H), 2.64-2.76 (m, 1H), 2.41-2.45 (m, 1H), 2.11-2.21 (m, 1H), 1.85-1.96 (m, 1H), 1.56 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).
37	568.3	(DMSO-d_6) δ 10.64 (br s, 1H), 9.32 (s, 2H), 8.77 (d, J= 5.20 Hz, 1H), 8.41 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 7.36-7.42 (m, 1H), 6.88 (m, 1H), 5.16 (s, 1H), 3.76 (s, 2H), 3.12-3.25 (m, 4H), 2.72 (t, J= 11.20 Hz, 2H), 1.86-1.93 (m, 2H), 1.69 (m, 2H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).
38	578.31	(DMSO-d_6) δ 10.60 (br s, 1H), 9.33 (s, 2H), 8.61 (d, J= 5.60 Hz, 1H), 8.38 (s, 1H), 8.12 (s, 1H), 8.01 (s, 1H), 7.04 (m, 1H), 6.86 (m, 1H), 5.15 (s, 1H), 4.26 (t, J= 6.0 Hz, 2H), 3.57 (m, 4H), 3.17-3.24 (m, 2H), 2.44-2.46 (m, 2H), 2.37 (br s, 4H), 1.91-1.98 (m, 2H), 1.56 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).
39	436.19	(DMSO-d_6) δ 10.78 (br s, 1H), 9.81 (s, 1H), 9.36 (s, 2H), 8.89 (s, 1H), 8.71 (s, 1H), 8.56 (s, 1H), 8.22 (s, 1H), 6.92 (m, 1H), 5.16 (s, 1H), 3.21 (m, 2H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H)
40	437	($CDCl_3$) δ 9.04 (s, 2H), 8.79 – 8.71 (m, 1H), 8.04 – 7.76 (m, 4H), 7.31 – 7.26 (m, 3H), 4.94 (t, J = 4.5 Hz, 1H), 4.02 (ddd, J = 25.6, 11.5, 4.5 Hz, 2H), 3.34 (dd, J = 3.3, 1.6 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H).
41	429.98	($CDCl_3$) δ 8.87 (1 H, d, J = 1.8 Hz), 8.13 (1 H, dd, J = 8.2 and 1.8 Hz), 7.74 (1 H, s), 7.46 (1 H, d, J = 8.2 Hz), 3.87 (2 H, s), 3.46 (2 H, m), 2.44 (6 H, s), 1.64 (6 H, s), 1.30 (3 H, t, J = 7.2 Hz).
42	548.34	(DMSO-d_6) δ 9.32 (s, 2H), 8.75 (d, J= 5.20 Hz, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.12 (s, 1H), 7.41 (d, J= 4.80 Hz, 1H), 6.90 (m, 1H), 5.15 (s, 1H), 3.90 (m, 1H), 3.77 (s, 2H), 3.21 (m, 3H), 3.15 (s, 3H), 2.72-2.76 (m, 1H), 2.59-2.65 (m, 1H), 2.54 (m, 1H), 1.97-2.04 (m, 1H), 1.57-1.72 (m, 1H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).
43	450.24	(DMSO-d_6) δ 10.70 (br s, 1H), 9.34 (s, 2H), 9.27 (s, 1H), 8.55 (m, 2H), 8.25 (s, 1H), 6.83 (m, 1H), 5.16 (s, 1H), 3.21 (m, 2H), 2.60 (s, 3H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H)

44	471.96	($CDCl_3$) δ 10.8 (1 H, br s), 8.91 (1 H, d, J = 1.9 Hz), 8.11 (1 H, dd, J = 8.2 and 1.9 Hz), 7.78 (1 H, s), 7.48 (1 H, dd, J = 8.2 and 0.6 Hz), 4.98 (1 H, br s), 3.92 (2 H, s), 3.80 (4 H, br s), 3.47 (2 H, m), 2.70 (4 H, br s), 1.65 (6 H, s), 1.30 (3 H, t, J = 7.3 Hz).
45	574.20 $[M-H]^-$	(DMSO-d_6) δ 12.43 (br s, 1H), 10.82 (br s, 1H), 9.24 (s, 2H), 8.54 (s, 1H), 7.94-8.0 (m, 2H), 7.66 (s, 1H), 7.03 (m, 1H), 6.77 (m, 1H), 5.14 (br s, 1H), 4.01-4.04 (m, 2H), 3.15-3.25 (m, 4H), 2.0-2.04 (m, 2H), 1.55 (s, 6H), 1.40-1.45 (m, 2H), 1.19 (s, 3H) and 1.09 (t, J=7.20 Hz, 3H).
46	493.21	(DMSO-d_6) δ 10.74 (br s, 1H), 9.32 (s, 2H), 8.69 (s, 1H), 8.45 (d, J= 8.40 Hz, 1H), 8.36 (s, 1H), 8.12 (s, 1H), 7.89 (d, J= 8.40 Hz, 1H), 7.02 (m, 1H), 5.15 (s, 1H), 3.74 (s, 2H), 3.20-3.23 (m, 2H), 1.56 (s, 6H) and 1.11 (t, J=7.20 Hz, 3H).
47	475.1	($CDCl_3$) δ 10.25 (s, 1H), 9.26 (s, 2H), 8.64 (dd, J = 4.6, 0.7 Hz, 1H), 7.77 – 7.60 (m, 3H), 7.54 (d, J = 17.3 Hz, 2H), 7.21 – 7.08 (m, 1H), 3.11 (dd, J = 18.7, 11.4 Hz, 2H), 1.64 – 1.50 (m, 2H), 1.48 – 1.29 (m, 4H), 1.26 (t, J = 7.3 Hz, 4H), 0.97 (t, J = 7.1 Hz, 3H).
48	440.03	($CDCl_3$) δ 8.79 (d, J = 4.3 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 8.00 (s, 1H), 7.96 (d, J = 1.0 Hz, 1H), 7.89 (s, 1H), 7.86 (dd, J = 7.9, 1.7 Hz, 1H), 7.33 (dd, J = 6.8, 5.0 Hz, 1H), 3.44 -3.37 (m, 3H), 1.78 (s, 6H), 1.32 (t, J = 7.3 Hz, 3H).
49	435.12	(DMSO-d_6) δ 10.68 (s, 1H), 9.44 – 9.33 (m, 1H), 9.08 – 8.97 (m, 1H), 8.85 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.70 (d, J = 1.5 Hz, 1H), 8.52 – 8.38 (m, 2H), 8.09 – 7.97 (m, 1H), 7.49 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 3.29 – 3.13 (m, 2H), 1.56 (s, 6H), 1.14 (dd, J = 9.3, 5.0 Hz, 3H).
50	576.32	(DMSO-d_6) δ 10.88 (br s, 1H), 9.32 (s, 2H), 8.34 (d, J= 5.60 Hz, 1H), 8.31 (s, 1H), 8.06 (s, 1H), 7.71 (br s, 1H), 7.28 (br s, 1H), 6.89 (m, 1H), 5.15 (br s, 1H), 3.84-3.87 (m, 2H), 3.14-3.34 (m, 4H), 2.07-2.10 (m, 2H), 1.56 (s, 6H), 1.34-1.44 (m, 2H), 1.15 (s, 3H) and 1.11 (t, J= 7.20 Hz, 3H)
51	576.34	(DMSO-d_6) δ 12.40 (br s, 1H), 10.67 (br s, 1H), 9.29 (s, 2H), 8.21 (s, 1H), 8.07 (s, 1H), 7.67-7.71 (m, 1H), 7.62-7.64 (m, 1H), 6.93 (m, 1H), 6.89 (m, 1H), 5.13 (s, 1H), 4.14-4.17 (m, 2H), 3.38 (m, 2H), 3.21-3.24 (m, 2H), 2.07-2.11 (m, 2H), 1.56 (s, 6H), 1.45-1.50 (m, 2H), 1.19 (s, 3H) and 1.12 (t, J=7.20 Hz, 3H).
52	577.38	(DMSO-d_6) δ 12.50 (br s, 1H), 10.66 (br s, 1H), 9.22 (s, 2H), 8.61 (s, 1H), 8.42 (d, J= 6.0 Hz, 1H), 8.15 (s, 1H), 6.86-6.88 (m, 2H), 5.14 (s, 1H), 4.26-4.32 (m, 2H), 3.38 (m, 2H), 3.21-3.24 (m, 2H), 2.08-2.11 (m, 2H), 1.56 (s, 6H), 1.44-1.49 (m, 2H), 1.20 (s, 3H) and 1.14 (t, J=7.20 Hz, 3H)

53	504.11	($CDCl_3$) δ 9.16 (s, 2H), 8.64 (s, 1H), 8.00 (s, 2H), 7.84 (s, 1H), 7.24 (d, J = 3.2 Hz, 1H), 4.02 (s, 2H), 3.64 – 3.19 (m, 2H), 2.29 (s, 1H), 1.62 (s, 6H), 1.28 (dd, J = 14.6, 7.4 Hz, 4H), 0.56 (d, J = 5.5 Hz, 3H).
54	590.34	(DMSO-d_6) δ 12.20 (br s, 1H), 10.55 (br s, 1H), 9.28 (s, 2H), 8.20 (d, J= 6.0 Hz, 1H), 8.06-8.11 (m, 2H), 7.36 (s, 1H), 6.89 (m, 1H), 6.55 (m, 2H), 5.15 (s, 1H), 3.50-3.52 (m, 2H), 3.15-3.24 (m, 2H), 2.50 (m, 1H), 2.03-2.10 (m, 2H), 1.86-1.94 (m, 2H), 1.56 (s, 6H), 1.29-1.38 (m, 2H) and 1.09-1.13 (m, 6H).
55	520.25	(DMSO-d_6) δ 10.70 (br s, 1H), 9.32 (s, 2H), 8.75 (d, J= 4.40 Hz,1H), 8.37-8.42 (m, 2H), 8.12 (s, 1H), 7.43 (d, J= 4.40 Hz, 1H), 6.87 (m, 1H), 5.30 (d, J= 5.20 Hz,1H), 4.86 (m, 1H), 3.61-3.70 (m, 6H), 3.19 (m, 2H), 2.43-2.45 (m, 4H), 1.47 (d, J= 6.40 Hz, 3H) and 1.11 (t, J=7.20 Hz, 3H).
56	564.31	(DMSO-d_6) δ 10.60 (br s, 1H), 9.31 (s, 2H), 8.52 (s, 1H), 8.45 (d, J= 8.80 Hz, 1H), 8.29 (s, 1H), 8.07 (s, 1H), 7.62 (m, 1H), 6.86 (m, 1H), 5.15 (s, 1H), 4.30 (t, J= 5.60 Hz, 2H), 3.59 (br s, 4H), 3.21 (m, 2H), 2.75 (t, J= 5.60 Hz, 2H), 2.45-2.50 (m, 4H), 1.56 (s, 6H) and 1.09 (t, J= 7.20 Hz, 3H).
57	449.11	(DMSO-d_6) δ = 10.58 (bs, 1H), 9.35 (s, 2H), 8.84 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 1.3 Hz, 1H), 8.10–7.98 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.92 (bt, J = 5.5 Hz, 1H), 5.15 (s, 1H), 3.18 (dd, J = 13.0, 6.7 Hz, 2H), 1.59 (s, 6H), 1.53 (dd, J = 14.2, 7.3 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H).
58	447.1	(DMSO-d_6) δ 10.61 (s, 1H), 9.32 (s, 2H), 8.83 (d, J = 4.0 Hz, 1H), 8.53 (d, J = 8.2 Hz, 1H), 8.40 (d, J = 1.1 Hz, 1H), 8.14 (s, 1H), 8.02 (td, J = 8.1, 1.7 Hz, 1H), 7.46 (dd, J = 7.0, 5.2 Hz, 1H), 6.86 (d, J = 5.3 Hz, 1H), 5.28 (d, J = 6.0 Hz, 1H), 3.38 (dd, J = 14.0, 7.0 Hz, 2H), 1.42 – 1.28 (m, 1H), 1.12 (t, J = 7.0 Hz, 3H), 0.54 – 0.46 (m, 2H), 0.46 – 0.33 (m, 2H).
59	435.1	(DMSO-d_6) δ 10.62 (s, 1H), 9.32 (s, 2H), 8.90 – 8.76 (m, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.39 (d, J = 1.5 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 8.02 (td, J = 7.8, 1.8 Hz, 1H), 7.46 (ddd, J = 7.5, 4.9, 0.8 Hz, 1H), 6.87 (t, J = 5.3 Hz, 1H), 5.21 (d, J = 5.9 Hz, 1H), 4.63 (dt, J = 11.7, 5.8 Hz, 1H), 3.27 – 3.16 (m, 2H), 1.98 – 1.73 (m, 2H), 1.18 – 1.06 (m, 3H), 0.90 (t, J = 7.4 Hz, 3H).
60	463.1	(DMSO-d_6) δ 10.62 (s, 1H), 9.33 (s, 2H), 8.83 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 8.08 – 7.95 (m, 1H), 7.46 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.86 (t, J = 5.5 Hz, 1H), 5.02 (d, J = 6.7 Hz, 1H), 4.44 (d, J = 6.8 Hz, 1H), 3.26 – 3.18 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H), 0.95 (s, 9H).

61	449.1	(DMSO-d_6) δ 10.59 (s, 1H), 9.32 (s, 2H), 8.83 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.4 Hz, 1H), 8.07 – 7.97 (m, 1H), 7.46 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.20 (d, J = 6.0 Hz, 1H), 4.70 (dt, J = 7.4, 5.8 Hz, 1H), 3.26 – 3.18 (m, 2H), 1.93 – 1.69 (m, 2H), 1.50 – 1.27 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H).
62	520.06	(MeOD) δ 9.21 (s, 2H), 8.77 (d, J = 3.1 Hz, 1H), 8.47 (s, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 1.5 Hz, 1H), 8.00 (d, J = 1.5 Hz, 1H), 7.95 (td, J = 7.8, 1.8 Hz, 1H), 7.40 (dd, J = 7.0, 5.3 Hz, 1H), 6.04 (q, J = 6.8 Hz, 1H), 3.87 (s, 1H), 3.35 (t, J = 3.6 Hz, 2H), 1.75 (d, J = 6.8 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.12 (d, J = 7.0 Hz, 6H).
63	520.04	(MeOD) δ 9.21 (s, 2H), 8.82 – 8.74 (m, 1H), 8.47 (s, 1H), 8.29 (d, J = 8.2 Hz, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.96 (ddd, J = 11.0, 9.8, 1.7 Hz, 2H), 7.44 – 7.35 (m, 1H), 6.02 (q, J = 6.8 Hz, 1H), 3.90 (d, J = 4.4 Hz, 1H), 3.36 (t, J = 7.2 Hz, 2H), 1.75 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 7.2 Hz, 3H), 1.13 (dd, J = 7.0, 2.1 Hz, 6H).
64	522.3	(DMSO-d_6) δ 10.62 (br s, 1H), 9.32 (s, 2H), 8.75 (d, J= 4.40 Hz, 1H), 8.37-8.43 (m, 2H), 8.13 (s, 1H), 7.42 (br s, 1H), 6.86 (m, 1H), 5.29 (s, 2H), 4.87 (br s, 1H), 3.78 (s, 2H), 3.21 (m, 2H), 2.80-2.83 (m, 2H), 2.66 (m, 1H), 1.93-2.18 (m, 3H), 1.47 (d, J= 6.0 Hz, 3H) and 1.10 (t, J= 6.40 Hz, 3H).
65	506.23	(DMSO-d_6) δ 10.73 (br s, 1H), 9.32 (s, 2H), 8.72 (d, J= 4.80 Hz, 1H), 8.36 (m, 2H), 8.11 (s, 1H), 7.34 (m, 1H), 6.98 (m, 1H), 5.29-5.36 (m, 2H), 4.86-4.89 (m, 1H), 4.23 (m, 1H), 3.72 (s, 2H), 3.56 (m, 2H), 3.21 (m, 2H), 2.85 (m, 2H), 1.47 (d, J= 6.80 Hz, 3H) and 1.11 (t, J=7.20 Hz, 3H).
66	520.27	(DMSO-d_6) δ 10.62 (br s, 1H), 9.32 (s, 2H), 8.72 (d, J= 4.80 Hz, 1H), 8.36 (m, 2H), 8.12 (s, 1H), 7.37 (m, 1H), 6.68 (m, 1H), 5.29 (d, J =5.6 Hz, 1H), 5.22 (br s, 1H), 4.87 (m, 1H), 3.74 (s, 2H), 3.19-3.26 (m, 4H), 2.97 (m, 2H), 1.47 (t, J= 6.80 Hz, 3H), 1.38 (s, 3H) and 1.09 (t, J=7.20 Hz, 3H).
67	548.3	(DMSO-d_6) δ 12.18 (br s, 1H), 9.40 (s, 2H), 9.07 (s, 1H), 8.88 (br s, 1H), 8.58 (s, 1H), 8.20 (s, 1H), 7.65-7.70 (m, 1H), 7.28 (br s, 1H), 7.28 (s, 1H), 4.60 (m, 2H), 3.56 (m, 1H), 3.09-3.37 (m, 7H), 1.90- 2.01 (m, 2H) 1.57 (s, 6H) and 1.06-1.21 (m, 5H).
68	534.14	(DMSO-d_6) δ = 10.62 (s, 1H), 9.33 (s, 2H), 8.77 (d, J = 4.9 Hz, 1H), 8.42 (s, 1H), 8.37 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 7.47 (d, J = 5.1 Hz, 1H), 6.88 (t, J = 5.5 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.96–4.83 (m, 1H), 4.11 (d, J = 14.4 Hz, 1H), 3.67 (ddd, J = 10.7, 7.3, 3.2 Hz, 2H), 3.58–3.47 (m, 1H), 3.39 (d, J = 14.0 Hz, 1H), 3.27–3.19 (m, 3H), 2.61 (dt, J = 11.7, 2.6 Hz, 1H), 2.50-2.44 (m, 1H), 2.24 (ddd, J = 12.6, 9.8, 3.2 Hz, 1H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 1.06 (d, J = 6.3 Hz, 3H).

69	548.18	(DMSO-d_6) δ = 10.64 (s, 1H), 9.34 (s, 2H), 8.77 (d, J = 5.3 Hz, 1H), 8.43 (s, 1H), 8.38 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.4 Hz, 1H), 7.44 (dd, J = 5.0, 1.0 Hz, 1H), 6.90 (t, J = 5.4 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.97–4.83 (m, 1H), 3.70–3.57 (m, 4H), 3.28–3.17 (m, 2H), 2.75 (d, J = 10.2 Hz, 2H), 1.75 (t, J = 10.7 Hz, 2H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.3 Hz, 6H).
70	528.18	(DMSO-d_6) δ = 10.64 (bs, 1H), 9.34 (s, 2H), 8.84–8.71 (m, 1H), 8.43 (s, 1H), 8.38 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.4 Hz, 1H), 7.45 (dd, J = 5.1, 1.2 Hz, 1H), 6.90 (bt, J = 5.4 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.99–4.82 (m, 1H), 3.66 (s, 2H), 3.24 (tt, J = 12.9, 6.5 Hz, 2H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).
71	548.19	(DMSO-d_6) δ = 10.64 (bs, 1H), 9.33 (s, 2H), 8.77 (d, J = 5.0 Hz, 1H), 8.43 (d, J = 13.5 Hz, 1H), 8.37 (s, 1H), 8.14 (d, J = 1.1 Hz, 1H), 7.55–7.40 (m, 1H), 6.90 (bt, J = 5.3 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.97–4.81 (m, 1H), 4.18 (d, J = 14.5 Hz, 0.5H), 3.77 (d, J = 14.5 Hz, 0.5H), 3.73-3.50 (m, 3H), 3.28–3.17 (m, 3H), 2.86-2.76 (m, 0.5H), 2.72-2.59 (m, 0.5H), 2.45–2.29 (m, 1.5H), 1.86 (dd, J = 11.4, 10.3 Hz, 0.5H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 1.10-0.95 (m, 6H).
72	548.06	(DMSO-d_6) δ 9.32 (s, 2H), 8.80 – 8.75 (m, 1H), 8.44 (brs, 1H), 8.34 (d, J = 1.6 Hz, 1H), 8.13 (d, J = 1.5 Hz, 1H), 7.48 (d, J = 5.1 Hz, 1H), 7.08 (t, J = 5.1 Hz, 1H), 4.89 (q, J = 6.6 Hz, 1H), 4.13 (d, J = 14.1 Hz, 1H), 3.83 (d, J = 14.2 Hz, 1H), 3.28 – 3.20 (m, 5H), 3.11 – 2.98 (m, 2H), 2.14 (ddd, J = 16.5, 12.3, 8.2 Hz, 2H), 1.97 – 1.85 (m, 2H), 1.85 – 1.74 (m, 3H), 1.13 (dd, J = 9.4, 5.0 Hz, 3H).
73	532.15	(DMSO-d_6) δ 10.63 (s, 1H), 9.34 (s, 2H), 8.75 (d, J = 5.5 Hz, 1H), 8.49 – 8.27 (m, 2H), 8.14 (d, J = 1.5 Hz, 1H), 7.36 (d, J = 5.5 Hz, 1H), 6.88 (t, J = 5.5 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.99 – 4.83 (m, 1H), 4.64 (s, 4H), 3.68 (s, 2H), 3.41 (s, 4H), 3.23 (dd, J = 7.2, 5.8 Hz, 2H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).
74	576.19	(Acetone-d_6) δ 8.79 (s, 2H), 8.75 (dd, J = 5.2, 0.7 Hz, 1H), 8.49 (s, 1H), 8.22 (d, J = 1.6 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.58 (dd, J = 5.2, 1.6 Hz, 1H), 7.17 (s, 1H), 4.50 – 4.42 (m, 2H), 3.44 – 3.32 (m, 4H), 2.20 – 2.12 (m, 2H), 1.62 (s, 6H), 1.53 – 1.44 (m, 2H), 1.29 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H).
75	548.12 $[M-H]^-$	(DMSO-d_6) δ 10.96 (br s, 1H), 10.73 (br s, 1H), 9.32 (s, 2H), 8.68 (d, J= 5.60 Hz, 1H), 8.35 (s, 1H), 8.15 (s, 1H), 7.93 (s, 1H), 7.13 (d, J= 5.60 Hz, 1H), 7.00 (br s, 1H), 4.87 (m, 1H), 4.69 (m, 2H), 3.81 (m, 3H), 3.64 (m, 2H), 3.54-3.57 (m, 2H), 3.19-3.24 (m, 5H), 1.47 (t, J= 6.40 Hz, 3H) and 1.11 (t, J=7.20 Hz, 3H).

76	518.09 $[M-H]^-$	(DMSO-d_6) δ 10.62 (br s, 1H), 9.32 (s, 2H), 8.73 (d, J= 4.40 Hz, 1H), 8.37-8.39 (m, 2H), 8.13 (s, 1H), 7.36 (d, J= 4.40 Hz, 1H), 6.85 (m, 1H), 5.30 (d, J= 5.60 Hz, 1H), 4.86-4.91 (m, 1H), 4.02 (m, 1H), 3.76 (br s, 2H), 3.59 (m, 2H), 3.21 (m, 2H), 3.15 (s, 3H), 2.95 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H) and 1.09 (t, J=7.20 Hz, 3H).
77	518.11 $[M-H]^-$	(DMSO-d_6) δ 10.63 (br s, 1H), 9.32 (s, 2H), 8.74 (d, J= 4.80 Hz, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.12 (s, 1H), 7.41 (d, J= 4.80 Hz, 1H), 6.88 (m, 1H), 5.30 (d, J=5.20 Hz, 1H), 4.85-4.89 (m, 1H), 4.74 (d, J=4.40 Hz, 1H), 4.22 (m, 1H), 3.68-3.72 (m, 2H), 3.38 (m, 1H), 3.20-3.23 (m, 2H), 2.67-2.72 (m, 2H), 2.38-2.41 (m, 1H), 1.98-2.05 (m, 1H), 1.55-1.61 (m, 1H), 1.47 (d, J= 6.80 Hz, 3H) and 1.09 (t, J=7.20 Hz, 3H).
78	509.1	(DMSO-d_6) δ 10.63 (br s, 1H), 9.21 (s, 2H), 8.61 (s, 1H), 8.26 (d, J= 5.20 Hz, 1H), 8.20 (s, 1H), 7.82 (m, 1H), 6.84 (m, 1H), 6.55 (d, J= 5.60 Hz, 1H), 5.17 (s, 1H), 3.78 (m, 2H), 3.63 (m, 2H), 3.38 (s, 3H), 3.20 (m, 2H), 1.55 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H)
79	548.19	(DMSO-d_6 + D_2O): δ 9.32 (s, 2H), 8.68 (s, 1H), 8.56 (d, J= 6.80 Hz, 1H), 8.30 (s, 1H), 7.18 (d, J= 6.80 Hz, 1H), 3.67 (m, 4H), 3.18-3.22 (m, 6H), 2.34 (m, 2H), 1.55 (s, 6H), 1.29 (t, J= 7.20 Hz, 3H) and 1.09 (t, J= 7.20 Hz, 3H)
80	509.16	(DMSO-d_6 + D_2O): δ 9.31 (s, 2H), 8.65 (d, J= 5.20 Hz, 1H), 8.21-8.24 (m, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.23 (m, 1H), 4.36-4.45 (m, 2H), 3.74 (m, 2H), 3.36 (s, 3H), 3.14-3.18 (m, 2H), 1.55 (s, 6H) and 1.10 (t, J= 7.20 Hz, 3H).
81	506.12	(DMSO-d_6) δ 10.63 (bs, 1H), 9.35 (s, 2H), 8.85 (dd, J = 4.8, 0.8 Hz, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.16 (d, J = 1.4 Hz, 1H), 8.04 (td, J = 7.9, 1.8 Hz, 1H), 7.56–7.41 (m, 1H), 6.88 (bs, 1H), 5.33 (d, J = 5.8 Hz, 1H), 4.93 (dd, J = 12.8, 5.7 Hz, 1H), 3.55 (t, J = 4.6 Hz, 4H), 3.29–3.18 (m, 2H), 2.88 (dd, J = 12.6, 5.5 Hz, 1H), 2.79–2.69 (m, 1H), 2.59-2.53 (m, 2H), 2.50–2.42 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H).
82	421.06	(DMSO-d_6) δ 10.97 (bs, 1H), 9.34 (s, 2H), 8.85 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 8.08–7.97 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 7.06 (bd, J = 4.3 Hz, 1H), 5.15 (s, 1H), 2.77 (d, J = 4.6 Hz, 3H), 1.59 (s, 6H).
83	407.07	(DMSO-d_6) δ 10.75 (bs, 1H), 9.34 (s, 2H), 8.91–8.79 (m, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.15 (s, 1H), 8.09–7.95 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.8 Hz, 1H), 6.80 (d, J = 3.7 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.99–4.78 (m, 1H), 2.78 (d, J = 4.5 Hz, 3H), 1.50 (d, J = 6.6 Hz, 3H).

84	534.13	(DMSO-d_6) δ 10.66 (br s, 1H), 9.32 (s, 2H), 8.74 (d, J= 4.80 Hz, 1H), 8.43 (br s, 1H), 8.37 (s, 1H), 8.13 (s, 1H), 7.44 (m, 1H), 6.92 (m, 1H), 5.30 (d, J=5.20 Hz, 1H), 4.86 (m, 1H), 4.62 (br s, 1H), 3.76 (br s, 2H), 3.33 (m, 2H), 3.20 (m, 2H), 2.59-2.75 (m, 2H), 1.76 (m, 2H), 1.47 (t, J= 6.40 Hz, 3H), 1.25 (s, 3H) and 1.09 (t, J=6.80 Hz, 3H).
85	495.19	(DMSO-d_6) δ 10.64 (br s, 1H), 9.21 (s, 2H), 8.61 (s, 1H), 8.24 (m, 1H), 8.15 (s, 1H), 7.76 (m, 1H), 6.86 (m, 1H), 6.54 (d, J= 6.0 Hz, 1H), 5.15 (s, 1H), 4.74 (m, 1H), 3.29 (m, 4H), 3.21 (m, 2H), 1.56 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H)
86	521.26	(DMSO-d_6) δ 10.62 (br s, 1H), 9.21 (s, 2H), 8.61 (s, 1H), 8.40 (d, J= 6.0 Hz, 1H), 8.19 (s, 1H), 6.91 (br s, 1H), 6.43 (d, J= 6.0 Hz, 1H), 5.84 (s, 1H), 5.15 (s, 1H), 4.10 (br s, 4H), 3.21 (m, 2H), 1.56 (s, 6H), 1.49 (s, 3H) and 1.12 (t, J= 7.20 Hz, 3H)
87	575.23 $[M-H]^-$	(DMSO-d_6) δ 12.54 (br s, 1H), 10.72 (br s, 1H), 9.33 (s, 2H), 8.71 (s, 1H), 8.43 (s, 1H), 8.15 (s, 1H), 7.69 (s, 1H), 6.99 (m, 1H), 5.15 (br s, 1H), 4.26-4.28 (m, 2H), 3.38 (m, 2H), 3.20 (m, 2H), 2.04-2.11 (m, 2H), 1.57 (s, 6H), 1.40-1.45 (m, 2H), 1.22 (s, 3H) and 1.11 (t, J= 7.20 Hz, 3H)
88	562.18	(Acetone-d_6) δ 8.80 (s, 2H), 8.76 (dd, J = 5.0, 0.6 Hz, 1H), 8.40 (s, 1H), 8.22 (d, J = 1.6 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.47 (dd, J = 5.1, 0.9 Hz, 1H), 5.02 (q, J = 6.5 Hz, 1H), 4.50 – 4.42 (m, 2H), 3.43 – 3.33 (m, 4H), 2.19 – 2.13 (m, 2H), 1.54 – 1.44 (m, 5H), 1.29 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H).
89	560.9	($CDCl_3$) δ 9.84 (br s, 1H), 9.06 (s, 2H), 8.56 (d, J = 4.2 Hz, 1H), 7.91 (dd, J = 11.7, 4.5 Hz, 2H), 7.83 – 7.67 (m, 2H), 7.55 (d, J = 12.7 Hz, 1H), 7.15 (dd, J = 7.1, 5.0 Hz, 1H), 3.72 (s, 2H), 3.59 – 3.40 (m, 4H), 2.47 (s, 4H), 2.36 (s, 3H), 1.90 (s, 6H), 1.31 (t, J = 7.2 Hz, 3H).
90	435.16 $[M-H]^-$	(DMSO-d_6) δ 10.85 (br s, 1H), 10.61 (br s, 1H), 9.30 (s, 2H), 8.50 (m, 1H), 8.34 (s, 1H), 8.09 (s, 1H), 7.80 (s, 1H), 6.87 (m, 2H), 5.31 (d, J= 5.60 Hz, 1H), 4.88 (m, 1H), 3.21 (m, 2H), 1.47 (d, J= 6.40 Hz, 3H) and 1.11 (t, J= 7.20 Hz, 3H)
91	564.24	(DMSO-d_6 + D_2O): δ 9.25 (s, 2H), 8.55 (s, 1H), 8.24 (s, 2H), 6.80 (s, 1H), 4.09 (s, 2H), 3.91 (br s, 2H), 3.76 (br s, 2H), 3.58 (br s, 4H), 3.16-3.24 (m, 4H), 1.54 (s, 6H) and 1.08 (t, J= 7.20 Hz, 3H)
92	495.27	(DMSO-d_6) δ 10.59 (br s, 1H), 9.33 (s, 2H), 8.61 (m, 1H), 8.40 (s, 1H), 8.12 (s, 1H), 8.05 (s, 1H), 7.05 (d, J= 5.20 Hz, 1H), 6.86 (m, 1H), 5.30 (d, J= 5.20 Hz, 1H), 4.87 (m, 1H), 4.36 (m, 2H), 3.73 (m, 2H), 3.33 (s, 3H), 3.21 (m, 2H), 1.49 (d, J= 6.40 Hz, 3H) and 1.11 (t, J= 7.20 Hz, 3H).

93	507.17	(DMSO-d_6) δ 10.62 (br s, 1H), 9.20 (s, 2H), 8.60 (s, 1H), 8.42 (d, J= 6.0 Hz, 1H), 8.16 (s, 1H), 6.85 (m, 1H), 6.44 (d, J= 5.60 Hz, 1H), 5.33 (d, J= 5.60 Hz, 1H), 4.86 (t, J= 6.40 Hz, 1H), 4.45 (m, 3H), 4.04 (br s, 2H), 3.30 (s, 3H), 3.22 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H) and 1.11 (t, J= 7.20 Hz, 3H)
94	507.27	(DMSO-d_6) δ 10.65 (br s, 1H), 9.22 (s, 2H), 8.61 (s, 1H), 8.48 (d, J= 6.0 Hz, 1H), 8.16 (s, 1H), 6.85-6.88 (m, 2H), 5.31 (d, J= 5.60 Hz, 1H), 4.88 (m, 1H), 3.75-3.81 (m, 8H), 3.22 (m, 2H), 1.48 (d, J= 6.80 Hz, 3H) and 1.11 (t, J= 7.20 Hz, 3H)
95	420.28	(DMSO-d_6) δ 10.61 (br s, 1H), 8.99 (s, 1H), 8.81 (m, 1H), 8.51 (d, J= 8.0 Hz, 1H), 8.30 (m, 2H), 7.98-8.02 (m, 2H), 7.62 (m, 1H), 7.45 (m, 1H), 6.86 (m, 1H), 5.45 (d, J= 4.40 Hz, 1H), 4.81 (q, J= 5.60 Hz, 1H), 3.21 (m, 2H), 1.43 (d, J= 6.40 Hz, 3H) and 1.11 (t, J= 7.20 Hz, 3H)
96	474.2	(DMSO-d_6) δ 10.63 (br s, 1H), 9.11 (s, 1H), 8.83 (m, 1H), 8.53 (d, J= 8.0 Hz, 1H), 8.42 (m, 1H), 8.35 (s, 1H), 8.07 (s, 1H), 8.0 (m, 1H), 7.75 (d, J= 8.0 Hz, 1H), 7.44 (m, 1H), 7.10 (m, 1H), 6.85 (br s, 1H), 5.22 (m, 1H), 3.21 (m, 2H) and 1.11 (t, J= 6.8 Hz, 3H)
97	577.37	(DMSO-d_6) δ 12.53 (br s, 1H), 10.67 (br s, 1H), 9.23 (s, 2H), 8.62 (s, 1H), 8.42 (br s, 1H), 8.16 (s, 1H), 6.88 (m, 2H), 5.16 (br s, 1H), 4.32 (m, 2H), 3.37 (m, 2H), 3.22 (m, 2H), 2.07-2.11 (m, 2H), 1.56 (s, 6H), 1.44-1.49 (m, 2H), 1.20 (s, 3H) and 1.12 (t, J= 7.20 Hz, 3H)
98	463.11	(DMSO-d_6) δ 10.64 (br s, 1H), 9.37 (s, 2H), 8.83 (br d, J = 3.9 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.16 (s, 1H), 8.02 (td, J = 7.9, 1.8 Hz, 1H), 7.46 (dd, J = 7.1, 5.2 Hz, 1H), 6.85 (t, J = 5.4 Hz, 1H), 4.89 (s, 1H),
99	576.22	(Acetone-d_6) δ 8.79 (s, 2H), 8.75 (dd, J = 5.2, 0.7 Hz, 1H), 8.49 (s, 1H), 8.22 (d, J = 1.6 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.58 (dd, J = 5.2, 1.6 Hz, 1H), 4.46 (dt, J = 13.8, 4.2 Hz, 2H), 3.43 – 3.33 (m, 4H), 2.20 – 2.13 (m, 2H), 1.62 (s, 6H), 1.53 – 1.44 (m, 2H), 1.29 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H).
100	571.08	(DMSO-d_6) δ 10.62 (s, 1H), 9.39 (s, 2H), 8.92 – 8.76 (m, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.17 (d, J = 1.1 Hz, 1H), 8.04 (td, J = 7.8, 1.8 Hz, 1H), 7.48 (ddd, J = 7.4, 4.9, 0.8 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.30 (s, 1H), 3.84 (td, J = 11.0, 2.2 Hz, 2H), 3.79 – 3.69 (m, 2H), 3.29 – 3.18 (m, 2H), 2.33 – 2.21 (m, 2H), 1.78 (d, J = 12.1 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
101	535.21	(DMSO-d_6) δ 11.51 (br s, 1H), 10.96 (br s, 1H), 9.37 (s, 2H), 9.17 (d, J= 4.80 Hz, 1H), 8.97 (s, 1H), 8.30 (s, 1H), 7.74 (d, J= 4.80 Hz, 1H), 7.14 (m, 1H), 4.75 (s, 2H), 4.00 (br s, 4H), 3.62-3.64 (m, 2H), 3.35 (br s, 2H), 3.21 (m, 2H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H).

102	535.22	(DMSO-d_6 + D_2O): δ 9.77 (s, 1H), 9.34 (s, 2H), 8.88 (s, 1H), 8.53 (s, 1H), 8.21 (s, 1H), 4.68 (s, 2H), 4.03 (br s, 2H), 3.85 (br s, 2H), 3.60 (br s, 2H), 3.49 (br s, 2H), 3.20 (m, 2H), 1.55 (s, 6H) and 1.09 (t, J= 7.20 Hz, 3H)
103	523.24	(DMSO-d_6) δ 10.64 (br s, 1H), 9.21 (s, 2H), 8.62 (s, 1H), 8.24 (d, J= 5.60 Hz, 1H), 8.14 (s, 1H), 7.57 (m, 1H), 6.81 (m, 1H), 6.65 (d, J= 6.0 Hz, 1H), 5.17 (s, 1H), 4.53 (s, 1H), 3.67 (d, J= 5.20 Hz, 1H), 3.36 (m, 1H), 3.20 (m, 2H), 1.55 (s, 6H), 1.23 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H)
104	521.2	(DMSO-d_6) δ 10.64 (br s, 1H), 9.33 (s, 2H), 8.60 (d, J= 5.60 Hz, 1H), 8.38 (s, 1H), 8.12 (s, 1H), 8.03 (s, 1H), 7.05 (m, 1H), 6.95 (m, 1H), 4.84-4.89 (m, 1H), 4.18-4.24 (m, 3H), 3.79-3.84 (m, 2H), 3.67-3.73 (m, 1H), 3.19-3.27 (m, 2H), 2.01-2.13 (m, 1H), 1.85-1.93 (m, 2H), 1.70-1.73 (m, 1H), 1.49 (d, J= 6.40 Hz, 3H) and 1.11 (t, J= 7.20 Hz, 3H).
105	493.15	(DMSO-d_6) δ 10.61 (br s, 1H), 9.20 (s, 2H), 8.61 (s, 1H), 8.40 (d, J= 6.0 Hz, 1H), 8.16 (s, 1H), 6.83 (m, 1H), 6.42 (d, J= 6.0 Hz, 1H), 5.90 (d, J= 6.80 Hz, 1H), 5.32 (d, J= 5.60 Hz, 1H), 4.88 (m, 1H), 4.70 (m, 1H), 4.52 (br s, 2H), 4.09 (br s, 2H), 3.21 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H) and 1.11 (t, J= 7.20 Hz, 3H)
106	525.22	(DMSO-d_6) δ 10.67 (br s, 1H), 9.21 (s, 2H), 8.52-8.54 (m, 2H), 8.16 (s, 1H), 6.82 (m, 1H), 5.30 (d, J= 5.60 Hz, 1H), 4.86 (m, 1H), 3.86 (m, 4H), 3.80 (m, 4H), 3.20 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H) and 1.11 (t, J= 7.20 Hz, 3H)
107	578.28	(DMSO-d_6 + D_2O): δ 9.29 (s, 2H), 8.59 (s, 1H), 8.52 (d, J= 6.40 Hz, 1H), 8.22 (s, 1H), 7.06 (d, J= 6.80 Hz, 1H), 3.56-3.79 (m, 8H), 3.37 (m, 2H), 3.33 (s, 3H), 3.21 (m, 2H), 2.50 (m, 2H), 1.54 (s, 6H) and 1.09 (t, J= 7.20 Hz, 3H)
108	573.21	(DMSO-d_6) δ 10.62 (br s, 1H), 9.11 (s, 1H), 8.76 (d, J= 4.80 Hz, 1H), 8.41 (m, 2H), 8.33 (s, 1H), 8.06 (s, 1H), 7.76 (d, J= 8.0 Hz, 1H), 7.44 (m, 1H), 7.10 (m, 1H), 6.85 (m, 1H), 5.22 (m, 1H), 3.64 (s, 2H), 3.61 (m, 4H), 3.21 (m, 2H), 2.43 (m, 4H) and 1.11 (t, J= 6.8 Hz, 3H)
109	563.25	(DMSO-d_6) δ 10.97 (br s, 1H), 9.38 (s, 2H), 8.69 (br s, 1H), 8.41 (s, 1H), 8.14 (s, 1H), 7.66 (br s, 1H), 7.22 (m, 1H), 5.29 (m, 1H), 4.88 (m, 1H), 4.28 (m, 2H), 3.20 (m, 2H), 2.06 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H), 1.33 (m, 2H), 1.22 (m, 2H) and 1.09-1.12 (m, 6H)
110	562.22	(DMSO-d_6) δ 12.29 (br s, 1H), 10.55 (br s, 1H), 9.32 (s, 2H), 8.37 (d, J= 6.0 Hz, 1H), 8.32 (s, 1H), 8.06 (s, 1H), 7.74 (br s, 1H), 6.91 (m, 2H), 5.14 (br s, 1H), 4.08-4.11 (m, 2H), 3.16-3.22 (m, 2H), 3.02-3.07 (m, 2H), 2.55 (m, 1H), 1.91-1.94 (m, 2H), 1.60-1.62 (m, 2H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H)

111	477.09	(DMSO-d_6) δ 10.62 (s, 1H), 9.39 (s, 2H), 8.92 – 8.76 (m, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.17 (d, J = 1.1 Hz, 1H), 8.04 (td, J = 7.8, 1.8 Hz, 1H), 7.48 (ddd, J = 7.4, 4.9, 0.8 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.30 (s, 1H), 3.84 (td, J = 11.0, 2.2 Hz, 2H), 3.79 – 3.69 (m, 2H), 3.29 – 3.18 (m, 2H), 2.33 – 2.21 (m, 2H), 1.78 (d, J = 12.1 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
112	560.17	(DMSO-d_6) δ 10.62 (s, 1H), 9.33 (s, 2H), 8.76 (d, J = 5.0 Hz, 1H), 8.44 – 8.32 (m, 2H), 8.14 (s, 1H), 7.42 (d, J = 4.9 Hz, 1H), 6.88 (t, J = 5.3 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.89 (p, J = 6.5 Hz, 1H), 4.28 (d, J = 5.6 Hz, 4H), 3.60 (s, 2H), 3.24 (dt, J = 14.0, 7.0 Hz, 2H), 2.34 (s, 4H), 1.83 (d, J = 4.9 Hz, 4H), 1.50 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).
113	449.05	(DMSO-d_6) δ 10.63 (s, 1H), 9.45 (s, 2H), 8.89 – 8.80 (ddd, J = 4.8, 1.7, 0.6 Hz 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.44 (d, J = 1.4 Hz, 1H), 8.20 (d, J = 1.4 Hz, 1H), 8.04 (td, J = 8.0, 1.7 Hz, 1H), 7.56 – 7.44 (ddd, J = 12.2, 4.8, 0.6 Hz, 1H), 6.87 (t, J = 5.2 Hz, 1H), 6.42 (s, 1H), 5.08 (d, J = 6.7 Hz, 2H), 4.77 (d, J = 6.7 Hz, 2H), 3.28 – 3.20 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H).
114	546.21 $[M-H]^-$	(DMSO-d_6) δ 10.61 (br s, 1H), 9.33 (s, 2H), 8.73 (m, 1H), 8.38 (d, J= 6.40 Hz, 2H), 8.13 (s, 1H), 7.37 (m, 1H), 6.85 (m, 1H), 5.15 (s, 1H), 3.75 (s, 2H), 3.18 -3.23 (m, 4H), 3.10 (s, 3H), 3.06 (m, 2H), 1.57 (s, 6H), 1.40 (s, 3H) and 1.09 (t, J= 7.20 Hz, 3H).
115	422.2	(DMSO-d_6) δ 10.74 (br s, 1H), 9.23 (s, 2H), 9.09 (d, J= 4.80 Hz, 2H), 8.71 (s, 1H), 8.23 (s, 1H), 7.57 (t, J= 4.80 Hz, 1H), 6.86 (m, 1H), 5.33 (d, J= 5.60 Hz, 1H), 4.87 (m, 1H), 3.22 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H) and 1.12 (t, J= 7.20 Hz, 3H)
116	603.3	(DMSO-d_6) δ 10.64 (br s, 1H), 9.11 (s, 1H), 8.74 (d, J= 4.0 Hz, 1H), 8.42 (m, 2H), 8.38 (s, 1H), 8.06 (m, 1H), 7.76 (d, J= 7.6 Hz, 1H), 7.36 (m, 1H), 7.12 (m, 1H), 6.86 (m, 1H), 5.22 (m, 1H), 4.02 (m, 1H), 3.76 (s, 2H), 3.58 (br s, 2H), 3.21 (m, 2H), 3.15 (s, 3H), 2.95 (br s, 2H) and 1.11 (t, J= 7.20 Hz, 3H)
117	563.31	(DMSO-d_6) δ 12.70 (br s, 1H), 10.92 (br s, 1H), 9.35 (s, 2H), 8.72 (br s, 1H), 8.45 (m, 1H), 8.35 (s, 1H), 7.12 (m, 1H), 7.02 (m, 1H), 4.88 (m, 1H), 3.54 (m, 2H), 3.22 (m, 2H), 2.53 (m, 3H), 2.20 (m, 2H), 1.57 (m, 2H), 1.49 (d, J= 6.40 Hz, 3H), 1.24 (s, 3H) and 1.12 (t, J= 7.20 Hz, 3H)
118	451.1	(DMSO-d_6) δ 10.62 (s, 1H), 9.33 (s, 2H), 8.83 (d, J = 4.2 Hz, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.39 (s, 1H), 8.14 (s, 1H), 8.02 (t, J = 7.6 Hz, 1H), 7.54 – 7.40 (m, 1H), 6.80 (d, J = 54.2 Hz, 1H), 5.06 (d, J = 6.5 Hz, 1H), 4.54 (d, J = 5.6 Hz, 1H), 4.49 (t, J = 5.7 Hz, 1H), 4.09 (dd, J = 11.5, 5.6 Hz, 1H), 3.28 – 3.16 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H), 1.07 (d, J = 6.3 Hz, 3H).

119	461.12	(DMSO-d_6) δ 10.61 (s, 1H), 9.32 (s, 2H), 8.83 (d, J = 4.1 Hz, 1H), 8.52 (d, J = 8.2 Hz, 1H), 8.39 (d, J = 1.4 Hz, 1H), 8.14 (s, 1H), 8.02 (td, J = 7.9, 1.7 Hz, 1H), 7.46 (dd, J = 7.2, 5.1 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.08 (s, 1H), 3.26
120	535.22	(DMSO-d_6) δ 10.72 (br s, 1H), 9.24 (s, 2H), 8.99 (s, 2H), 8.69 (s, 1H), 8.22 (s, 1H), 6.83 (m, 1H), 5.16 (s, 1H), 3.60-3.63 (m, 6H), 3.22 (m, 2H), 2.44 (br s, 4H), 1.56 (s, 6H) and 1.10 (t, J= 7.20 Hz, 3H).
121	520.13	(DMSO-d_6) δ 10.62 (s, 1H), 9.32 (s, 2H), 8.76 (d, J = 5.2 Hz, 1H), 8.42 (s, 1H), 8.36 (d, J = 1.6 Hz, 1H), 8.12 (d, J = 1.4 Hz, 1H), 7.44 (dd, J = 5.1, 1.0 Hz, 1H), 6.89 (t, J = 5.3 Hz, 1H), 5.28 (d, J = 5.6 Hz, 1H), 4.94 – 4.82 (m, 1H), 3.65 (s, 2H), 3.64 – 3.58 (m, 4H), 3.29 – 3.14 (m, 2H), 2.47 – 2.41 (m, 4H), 1.49 (d, J = 6.6 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).
122	520.13	(DMSO-d_6) δ 10.64 (s, 1H), 9.32 (s, 2H), 8.76 (d, J = 4.9 Hz, 1H), 8.42 (s, 1H), 8.36 (d, J = 1.6 Hz, 1H), 8.12 (d, J = 1.5 Hz, 1H), 7.44 (dd, J = 5.1, 1.0 Hz, 1H), 6.92 (s, 1H), 5.28 (d, J = 5.6 Hz, 1H), 4.88 (p, J = 6.5 Hz, 1H), 3.65 (s, 2H), 3.64 – 3.59 (m, 4H), 3.21 (dt, J = 12.8, 6.5 Hz, 2H), 2.47 – 2.40 (m, 4H), 1.49 (d, J = 6.6 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).
123	549.09	(DMSO-d_6) δ 10.67 (s, 1H), 9.43 (s, 2H), 8.85 (dd, J = 5.0, 0.9 Hz, 1H), 8.56 (d, J = 8.1 Hz, 1H), 8.44 (d, J = 1.4 Hz, 1H), 8.19 (d, J = 1.4 Hz, 1H), 8.04 (td, J = 8.1, 1.8 Hz, 1H), 7.48 (dd, J = 7.0, 5.0 Hz, 1H), 6.88 (s, 1H), 5.14 (d, J = 7.4 Hz, 2H), 4.93 (d, J = 7.4 Hz, 2H), 3.24 (m, 2H), 2.75 (t, J = 6.7 Hz, 2H), 2.57 (t, J = 6.7 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
124	551.12	(DMSO-d_6) δ 12.18 (s, 1H), 10.64 (s, 1H), 9.38 (s, 2H), 8.85 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 8.43 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H), 8.10 – 7.97 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.88 (t, J = 5.2 Hz, 1H), 5.47 (s, 1H), 4.50 (d, J = 10.6 Hz, 1H), 4.37 (d, J = 10.6 Hz, 1H), 3.23 (m, 2H), 2.50 – 2.38 (m, 4H), 1.58 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H).
125	576.18	(DMSO-d_6) δ 10.60 (s, 1H), 9.39 (s, 2H), 8.78 (d, J = 4.9 Hz, 1H), 8.45 (s, 1H), 8.41 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.46 (dd, J = 5.1, 1.0 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.30 (s, 1H), 3.84 (td, J = 11.0, 2.2 Hz, 2H), 3.77 – 3.70 (m, 2H), 3.66 (s, 2H), 3.65 – 3.60 (m, 4H), 3.24 (dd, J = 7.1, 5.8 Hz, 2H), 2.49 – 2.41 (m, 4H), 2.29 (td, J = 13.6, 4.8 Hz, 2H), 1.79 (d, J = 12.2 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
126	478.02	(DMSO-d_6) δ 9.38 (s, 2H), 8.84 (d, J = 3.7 Hz, 1H), 8.59 – 8.43 (m, 4H), 8.39 (s, 1H), 8.16 (s, 1H), 8.04 (t, J = 7.4 Hz, 1H), 7.54 – 7.42 (m, 1H), 7.34 (brs, 1H), 6.08 – 5.92 (m, 1H), 4.01 – 3.86 (m, 2H), 3.27 – 3.18 (m, 2H), 1.70 (d, J = 6.6 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H).

127	493.11	(DMSO-d_6) δ 10.62 (s, 1H), 9.37 (s, 2H), 8.83 (d, J = 4.0 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.15 (br s, 1H), 8.02 (td, J = 7.9, 1.8 Hz, 1H), 7.47 (dd, J = 7.1, 5.2 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.23 (s, 1H), 3.28 – 3.18 (m, 2H), 3.14 – 2.97 (m, 2H), 2.55 – 2.51 (m, 2H), 2.36 – 2.25 (m, 2H), 2.09 – 1.99 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H).
128	490.1	(DMSO-d_6) δ 10.71 (br s, 1H), 9.38 (s, 2H), 8.87 – 8.83 (m, 1H), 8.55 (m, J = 8.4 Hz, 1H), 8.42 (d, J = 1.6 Hz, 1H), 8.23 (br s, 1H), 8.17 (d, J = 1.6 Hz, 1H), 8.06 – 8.01 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.96 (t, J = 5.5 Hz, 1H), 5.21 (s, 1H), 3.28 – 3.16 (m, 4H), 2.71 – 2.61 (m, 2H), 2.36 – 2.23 (m, 5H), 1.83 (br d, J = 12.3 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
129	535.11	(DMSO-d_6) δ 10.80 (br s, 1H), 9.60 (br s, 2H), 9.36 (s, 2H), 8.85 (d, J = 4.7 Hz, 1H), 8.54 (d, J = 7.8 Hz, 1H), 8.40 (s, 1H), 8.26 (br s, 3H), 8.16 (s, 1H), 8.04 (t, J = 7.8 Hz, 1H), 7.49 (dd, J = 7.0, 4.7 Hz, 1H), 7.11 (br s, 1H), 4.19 (s, 2H), 3.29 – 3.16 (m, 6H), 1.87 (s, 6H), 1.13 (t, J = 7.1 Hz, 3H).
130	487.1	($CDCl_3$) δ 8.98 (s, 2H), 8.63 (d, J = 23.2 Hz, 1H), 8.01 – 7.64 (m, 4H), 7.24 – 7.19 (m, 1H), 6.14 – 5.66 (m, 1H), 4.92 (d, J = 55.8 Hz, 1H), 4.29 – 4.10 (m, 1H), 3.29 – 3.23 (m, 2H), 1.11 (t, J = 6.7 Hz, 3H).
131	505.1	($CDCl_3$) δ 9.08 (s, 2H), 8.78 (d, J = 4.4 Hz, 1H), 8.07 – 7.76 (m, 4H), 7.34 – 7.27 (m, 1H), 5.20 (s, 1H), 4.67 (d, J = 7.1 Hz, 1H), 3.48 – 3.36 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H).
132	505.88	(DMSO-d_6) δ 10.81 (bs, 1H), 9.37 (s, 2H), 8.84 (d, J = 4.1 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.47–8.29 (m, 4H), 8.16 (d, J = 1.3 Hz, 1H), 8.04 (t, J = 7.7 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.11 (bs, 1H), 4.25–4.06 (m, 1H), 3.29–3.13 (m, 2H), 1.91 (s, 3H), 1.81 (s, 3H), 1.54 (d, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H).
133	521.09	(DMSO-d_6) δ 10.75 (s, 1H), 9.33 (s, 2H), 8.86 – 8.79 (m, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.6 Hz, 1H), 8.06 – 7.97 (m, 1H), 7.50 – 7.42 (m, 1H), 6.99 (s, 1H), 5.85 (q, J = 6.7 Hz, 1H), 3.22 (dd, J = 7.1, 5.7 Hz, 2H), 2.69 – 2.59 (m, 2H), 2.55 (dd, J = 13.1, 6.8 Hz, 2H), 1.61 (d, J = 6.8 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).
134	521.1	(DMSO-d_6) δ 10.80 (s, 1H), 9.33 (s, 2H), 8.82 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.6 Hz, 1H), 8.06 – 7.97 (m, 1H), 7.50 – 7.42 (m, 1H), 7.03 (s, 1H), 5.85 (q, J = 6.7 Hz, 1H), 3.22 (dd, J = 7.1, 5.7 Hz, 2H), 2.67 – 2.59 (m, 2H), 2.47 – 2.40 (m, 2H), 1.61 (d, J = 6.8 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).
135	550.18	(DMSO-d_6) δ 10.62 (s, 1H), 9.35 (s, 2H), 8.78 (d, J = 4.8 Hz, 1H), 8.44 (s, 1H), 8.39 (s, 1H), 8.15 (s, 1H), 7.45 (d, J = 4.8 Hz, 1H), 6.88 (m, 1H), 5.04 (s, 1H), 4.68 (t, J = 6.0 Hz, 1H), 3.82 – 3.70 (m, 2H), 3.66 (s, 2H), 3.63 (s, 4H), 3.24 (dd, J = 12.9, 6.8 Hz, 2H), 2.45 (s, 4H), 1.52 (s, 3H), 1.14 (t, J = 6.8 Hz, 3H).

136	506.06	(DMSO-d_6) δ 9.39 (s, 2H), 8.84 (d, J = 4.1 Hz, 1H), 8.69 (s, 3H), 8.54 (d, J = 8.1 Hz, 1H), 8.40 (d, J = 1.2 Hz, 1H), 8.17 (d, J = 1.3 Hz, 1H), 8.04 (t, J = 7.2 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.21 (s, 1H), 5.95 (q, J = 6.7 Hz, 1H), 3.28 – 3.17 (m, 2H), 1.70 (d, J = 6.7 Hz, 3H), 1.62 (s, 6H), 1.13 (t, J = 7.2 Hz, 3H).
137	492.05	(DMSO-d_6) δ 9.39 (s, 2H), 8.84 (d, J = 4.1 Hz, 1H), 8.69 (s, 3H), 8.54 (d, J = 8.1 Hz, 1H), 8.40 (d, J = 1.2 Hz, 1H), 8.17 (d, J = 1.3 Hz, 1H), 8.04 (t, J = 7.2 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.21 (s, 1H), 5.95 (q, J = 6.7 Hz, 1H), 3.28 – 3.17 (m, 2H), 1.70 (d, J = 6.7 Hz, 3H), 1.62 (s, 6H), 1.13 (t, J = 7.2 Hz, 3H).
138	576.2	(DMSO-d_6) δ 10.61 (s, 1H), 9.36 (s, 2H), 8.84 – 8.81 (m, 1H), 8.52 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.4 Hz, 1H), 8.04 – 7.99 (m, 1H), 7.48 – 7.44 (m, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.32 (s, 1H), 3.79 (d, J = 12.6 Hz, 2H), 3.30 – 3.18 (m, 4H), 2.10 (td, J = 13.0, 4.4 Hz, 2H), 1.79 (d, J = 12.7 Hz, 2H), 1.43 (s, 9H), 1.12 (t, J = 7.2 Hz, 3H).
139	509.1	(DMSO-d_6) δ 10.62 (br s, 1H), 9.38 (s, 2H), 8.85 – 8.81 (m, 1H), 8.52 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.15 (d, J = 1.5 Hz, 1H), 8.04 – 7.99 (m, 1H), 7.46 (ddd, J = 7.5, 4.9, 0.8 Hz, 1H), 6.92 – 6.86 (m, 1H), 5.60 (s, 1H), 3.27 – 3.18 (m, 2H), 3.03 – 2.94 (m, 4H), 2.48 – 2.41 (m, 2H), 2.35 – 2.23 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H).
140	520.07	(DMSO-d_6) δ 10.63 (s, 1H), 9.33 (s, 2H), 8.84 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.56 (d, J = 8.4 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.03 (dt, J = 7.6, 1.8 Hz 1H), 7.48 (ddd, J = 7.6, 4.9, 0.9 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 3.27 – 3.20 (m, 2H), 3.18 (s, 2H), 2.27 (s, 6H), 1.80 (s, 6H), 1.14 (t, J = 7.2 Hz, 3H).
141	562.13	(DMSO-d_6) δ 10.63 (s, 1H), 9.33 (s, 2H), 8.84 (ddd, J = 4.9, 1.7, 0.8 Hz, 1H), 8.56 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.03 (td, J = 7.7, 1.7 Hz, 1H), 7.48 (ddd, J = 7.7, 4.9, 0.8 Hz, 1H), 6.86 (t, J = 5.4 Hz, 1H), 3.61 – 3.54 (m, 4H), 3.25 (s, 2H), 3.23 (m, 2H), 2.54 (m, 4H), 1.80 (s, 6H), 1.14 (t, J = 7.2 Hz, 3H).
142	548.29	(DMSO-d_6) δ 10.60 (s, 1H) 9.32 (s, 2H), 8.75 (d, J = 5.2 Hz, 1H), 8.41 (s, 1H), 8.38 (d, J = 1.2 Hz, 1H), 8.12 (s, 1H), 7.42 (d, J = 5.2 Hz, 1H), 6.90 (t, J = 5.2 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.88 (p, J = 6.4 Hz, 1H), 3.61 (m, 4H), 3.22 (m, 2H), 2.72 (d, J = 10.8 Hz, 2H), 1.73 (t, J = 10.8 Hz, 2H), 1.48 (d, J = 6.4 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.4 Hz, 6H).
143	548.27	(DMSO-d_6) δ 10.60 (s, 1H) 9.32 (s, 2H), 8.75 (d, J = 5.2 Hz, 1H), 8.41 (s, 1H), 8.38 (d, J = 1.2 Hz, 1H), 8.12 (s, 1H), 7.42 (d, J = 5.2 Hz, 1H), 6.90 (t, J = 5.2 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.88 (p, J = 6.4 Hz, 1H), 3.61 (m, 4H), 3.22 (m, 2H), 2.72 (d, J = 10.8 Hz, 2H), 1.73 (t, J = 10.8 Hz, 2H), 1.48 (d, J = 6.4 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.4 Hz, 6H).

144	534	(DMSO-d_6) δ 10.86 (bs, 1H), 9.33 (s, 2H), 8.91–8.78 (m, 1H), 8.57 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 8.10–7.99 (m, 1H), 7.91 (s, 2H), 7.56–7.42 (m, 1H), 7.17 (bs, 1H), 3.32–3.14 (m, 2H), 2.80 (dd, J = 12.8, 6.5 Hz, 2H), 2.39 (t, J = 6.7 Hz, 2H), 1.79 (s, 6H), 1.69–1.50 (m, 4H), 1.14 (t, J = 7.2 Hz, 3H).
145	562.18	(DMSO-d_6) δ 10.83 (bs, 1H), 10.22 (bs, 1H), 9.34 (s, 2H), 8.85 (d, J = 4.0 Hz, 1H), 8.57 (d, J = 8.2 Hz, 1H), 8.41 (d, J = 1.5 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.09–7.97 (m, 1H), 7.49 (dd, J = 7.2, 5.0 Hz, 1H), 7.15 (bs, 1H), 3.22 (dd, J = 12.3, 6.9 Hz, 2H), 3.11 – 2.97 (m, 2H), 2.74 (d, J = 4.9 Hz, 6H), 2.41 (t, J = 7.1 Hz, 2H), 1.79 (s, 6H), 1.77–1.67 (m, 2H), 1.64–1.48 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H).
146	492.07	(DMSO-d_6) δ 10.87 (bs, 1H), 9.36 (s, 2H), 8.85 (d, J = 4.2 Hz, 1H), 8.54 (d, J = 8.1 Hz, 1H), 8.39 (d, J = 1.3 Hz, 1H), 8.33 (s, 2H), 8.16 (d, J = 1.3 Hz, 1H), 8.04 (t, J = 7.2 Hz, 1H), 7.49 (dd, J = 7.1, 5.0 Hz, 1H), 7.21 (bs, 1H), 3.89 (d, J = 5.5 Hz, 2H), 3.32–3.11 (m, 2H), 1.86 (s, 6H), 1.13 (t, J = 7.1 Hz, 3H).
147	540.22	(DMSO-d_6) δ 10.63 (br s, 1H), 9.33 (s, 2H), 8.76 (d, J= 4.40 Hz, 1H), 8.38-8.41 (m, 2H), 8.13 (s, 1H), 7.40 (m, 1H), 6.86 (m, 1H), 5.16 (s, 1H), 3.89 (s, 2H), 3.69-3.76 (m, 4H), 3.21 (m, 2H), 1.57 (s, 6H) and 1.09 (t, J= 7.20 Hz, 3H)
148	576.18	(DMSO-d_6) δ 10.63 (s, 1H), 9.44 (s, 2H), 8.78 (d, J = 5.0 Hz, 1H), 8.48 – 8.37 (m, 2H), 8.19 (d, J = 1.0 Hz, 1H), 7.45 (dd, J = 5.0, 1.0 Hz, 1H), 6.88 (t, J = 5.4 Hz, 1H), 6.42 (s, 1H), 5.08 (d, J = 6.7 Hz, 2H), 4.78 (d, J = 6.7 Hz, 2H), 3.69 – 3.59 (m, 4H), 3.29 – 3.18 (m, 2H), 2.75 (d, J = 10.5 Hz, 2H), 1.76 (t, J = 10.5 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.3 Hz, 6H).
149[a]	498.97 $[M-H]^-$	(DMSO-d_6) δ 9.08 (s, 2H), 8.61 (d, *J* = 4.2 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.86 (s, 1H), 7.82 (s, 1H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.49 (s, 1H), 7.21 (dd, *J* = 7.0, 5.1 Hz, 1H), 5.35 – 5.19 (m, 1H), 3.14 (dd, *J* = 13.2, 6.9 Hz, 2H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H).
154	548.18	(DMSO-d_6): δ 10.62 (s, 1H), 9.44 (s, 2H), 8.78 (d, J = 5.0 Hz, 1H), 8.55 – 8.33 (m, 2H), 8.19 (d, J = 1.1 Hz, 1H), 7.46 (d, J = 5.0 Hz, 1H), 6.88 (t, J = 5.5 Hz, 1H), 6.42 (s, 1H), 5.08 (d, J = 6.7 Hz, 2H), 4.78 (d, J = 6.7 Hz, 2H), 3.67 (s, 2H), 3.64 (t, J = 4.5 Hz, 4H), 3.28 – 3.19 (m, 2H), 2.48 – 2.42 (m, 4H), 1.14 (t, J = 7.2 Hz, 3H).
155	573.26	(DMSO-d_6): δ 10.64 (br s, 1H), 9.11 (s, 1H), 8.74 (d, J= 4.0 Hz, 1H), 8.42 (m, 2H), 8.38 (s, 1H), 8.06 (m, 1H), 7.76 (d, J= 7.6 Hz, 1H), 7.36 (m, 1H), 7.12 (m, 1H), 6.86 (m, 1H), 5.22 (m, 1H), 4.02 (m, 1H), 3.76 (s, 2H), 3.58 (br s, 2H), 3.21 (m, 2H), 3.15 (s, 3H), 2.95 (br s, 2H) and 1.11 (t, J= 7.20 Hz, 3H)

156	568.28	(DMSO-d_6): δ 10.62 (br s, 1H), 9.33 (s, 2H), 8.77 (d, J= 4.80 Hz, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 8.13 (s, 1H), 7.45 (d, J= 4.80 Hz, 1H), 6.85 (m, 1H), 5.15 (s, 1H), 3.72 (s, 2H), 3.21 (m, 2H), 2.56 (m, 4H), 2.04 (m, 4H), 1.57 (s, 6H) and 1.11 (t, J= 7.2 Hz, 3H)
157	451.09	(DMSO-d_6): δ 10.62 (s, 1H), 9.36 (s, 2H), 8.91 – 8.78 (m, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 1.4 Hz, 1H), 8.16 (d, J = 1.4 Hz, 1H), 8.09 – 7.97 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.8 Hz, 1H), 6.88 (t, J = 5.3 Hz, 1H), 5.04 (s, 1H), 4.66 (t, J = 6.1 Hz, 1H), 3.81 – 3.66 (m, 2H), 3.29 – 3.17 (m, 2H), 1.52 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H).
158	435.17	(DMSO-d_6): δ 10.64 (br s, 1H), 9.31 (s, 2H), 8.65 (s, 1H), 8.43 (d, J= 8.40 Hz, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.84 (d, J= 8.0 Hz, 1H), 6.90 (m, 1H), 5.31 (d, J= 5.60 Hz, 1H), 4.86 (m, 1H), 3.21 (m, 2H), 2.40 (s, 3H), 1.48 (d, J= 6.40 Hz, 3H) and 1.11 (t, J= 7.20 Hz, 3H)
159	547.31	(DMSO-d_6): δ 10.62 (br s, 1H), 9.33 (s, 2H), 8.75 (d, J= 4.80 Hz, 1H), 8.40 (m, 2H), 8.13 (s, 1H), 7.41 (d, J= 4.8 Hz, 1H), 6.88 (br s, 1H), 5.15 (s, 1H), 3.62 (s, 2H), 3.21 (m, 2H), 2.35-2.50 (m, 8H), 2.15 (s, 3H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H)
160	518.22	(DMSO-d_6): δ 10.16 (d, J = 4.8 Hz, 1H), 9.39 (s, 2H), 9.03 (d, J = 4.7 Hz, 1H), 8.85 (d, J = 4.0 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.41 (d, J = 1.5 Hz, 1H), 8.18 (d, J = 1.5 Hz, 1H), 8.04 (td, J = 8.0, 1.6 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.18 (s, 1H), 6.01 (q, J = 6.7 Hz, 1H), 4.61 – 4.44 (m, 1H), 3.37 – 3.17 (m, 4H), 2.45 – 2.28 (m, 1H), 2.18 (dq, J = 14.2, 7.3 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.72 (d, J = 6.7 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H).
161	518.15	(DMSO-d_6): δ 10.16 (d, J = 4.8 Hz, 1H), 9.39 (s, 2H), 9.03 (d, J = 4.7 Hz, 1H), 8.85 (d, J = 4.0 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.41 (d, J = 1.5 Hz, 1H), 8.18 (d, J = 1.5 Hz, 1H), 8.04 (td, J = 8.0, 1.6 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.18 (s, 1H), 6.01 (q, J = 6.7 Hz, 1H), 4.61 – 4.44 (m, 1H), 3.37 – 3.17 (m, 4H), 2.45 – 2.28 (m, 1H), 2.18 (dq, J = 14.2, 7.3 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.72 (d, J = 6.7 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H).
162	548.14	(DMSO-d_6): δ 10.41 (br s, 1H), 9.41 (s, 2H), 8.83 (dd, J = 4.8, 0.9 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.6 Hz, 1H), 8.17 (d, J = 1.4 Hz, 1H), 8.03 (td, J = 7.9, 1.8 Hz, 1H), 7.51 – 7.44 (m, 1H), 6.86 (t, J = 5.3 Hz, 1H), 6.44 (s, 1H), 4.40 (br s, 2H), 4.01 (d, J = 8.3 Hz, 2H), 3.28 – 3.17 (m, 2H), 1.42 (s, 9H), 1.12 (t, J = 7.2 Hz, 3H).
163	448.1	(DMSO-d_6): δ 10.64 (s, 1H), 9.49 (s, 2H), 9.19 (s, 1H), 8.84 (ddd, J = 4.8, 1.7, 0.9 Hz, 2H), 8.53 (d, J = 8.3 Hz, 1H), 8.43 (d, J = 1.6 Hz, 1H), 8.21 (d, J = 1.5 Hz, 1H), 8.08 – 7.99 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.92 (t, J = 5.5 Hz, 1H), 4.64 – 4.52 (m, 2H), 4.23 – 4.11 (m, 2H), 3.29 – 3.14 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H).

164	562.2	(DMSO-d_6): δ 10.63 (bs, 1H), 9.35 (s, 2H), 8.78 (d, J = 4.9 Hz, 1H), 8.43 (s, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.4 Hz, 1H), 7.44 (dd, J = 5.1, 1.0 Hz, 1H), 6.89 (t, J = 5.4 Hz, 1H), 5.15 (s, 1H), 3.76–3.52 (m, 4H), 3.29–3.17 (m, 2H), 2.75 (d, J = 10.2 Hz, 2H), 1.75 (t, J = 10.7 Hz, 2H), 1.59 (s, 6H), 1.14 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.3 Hz, 6H).
165	589.05	HCl salt (DMSO-d_6): δ 10.84 (bs, 1H), 9.82 (bs, 1H), 9.33 (s, 2H), 9.00 (t, J = 5.8 Hz, 1H), 8.85 (d, J = 4.1 Hz, 1H), 8.55 (d, J = 8.1 Hz, 2H), 8.40 (d, J = 1.3 Hz, 1H), 8.16 (d, J = 1.3 Hz, 1H), 8.04 (t, J = 7.1 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.17 (bs, 1H), 4.24–4.16 (m, 2H), 4.03 (qd, J = 17.8, 5.9 Hz, 2H), 3.22 (dd, J = 17.0, 10.5 Hz, 4H), 2.30 (dd, J = 17.4, 9.5 Hz, 1H), 1.87 (t, J = 7.9 Hz, 2H), 1.81 (d, J = 3.1 Hz, 6H), 1.13 (t, J = 7.2 Hz, 3H).
166	531.92	HCl salt (DMSO-d_6): δ 10.87 (bs, 1H), 10.07 (bs, 1H), 9.37 (s, 2H), 8.85 (d, J = 4.1 Hz, 2H), 8.59–8.50 (m, 1H), 8.41 (d, J = 1.0 Hz, 1H), 8.17 (d, J = 1.1 Hz, 1H), 8.04 (t, J = 7.3 Hz, 1H), 7.49 (dd, J = 7.0, 4.8 Hz, 1H), 7.20 (s, 1H), 4.56–4.40 (m, 1H), 3.32–3.13 (m, 4H), 2.45–2.21 (m, 2H), 1.98 (dd, J = 13.1, 6.7 Hz, 2H), 1.92 (s, 3H), 1.81 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H).
167	676.25	(DMSO-d_6): δ 12.35 (s, 1H), 10.70 (s, 1H), 9.44 (s, 2H), 8.78 (d, J = 5.5 Hz, 1H), 8.46 (s, 1H), 8.42 (d, J = 1.4 Hz, 1H), 8.18 (d, J = 1.4 Hz, 1H), 7.45 (d, J = 5.5 Hz, 1H), 6.93 (s, 1H), 5.14 (d, J = 7.5 Hz, 2H), 4.94 (d, J = 7.5 Hz, 2H), 3.68 – 3.59 (m, 4H), 3.27 – 3.19 (m, 2H), 2.74 (m, 4H), 2.57 (m, 2H), 1.76 (t, J = 10.7 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.3 Hz, 6H).
168	465.21	(Acetone) δ 9.26 (s, 2H), 8.85 (d, J = 2.2 Hz, 1H), 8.85 (d, J = 2.2 Hz, 1H), 8.42 (d, J = 8.2 Hz, 1H), 8.35 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 8.01 (dd, J = 8.6, 2.0 Hz, 1H), 7.21 (d, J = 24.2 Hz, 1H), 5.05 (q, J = 6.7 Hz, 1H), 4.96 – 4.89 (m, 1H), 4.53 (s, 1H), 4.38 (d, J = 5.2 Hz, 1H), 1.54 (dd, J = 6.6, 4.4 Hz, 6H), 1.21 (t, J = 7.2 Hz, 3H).
169	605.12	(DMSO-d_6): δ 10.63 (s, 1H), 9.33 (s, 2H), 8.84 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 8.55 (d, J = 7.9 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.14 (d, J = 1.5 Hz, 1H), 8.08 – 7.98 (m, 1H), 7.48 (ddd, J = 7.9, 4.8, 0.8 Hz, 1H), 6.90 (t, J = 5.4 Hz, 1H), 3.56 – 3.52 (m, 4H), 3.39 (s, 2H), 3.28 – 3.20 (m, 2H), 2.63 (t, J = 6.2 Hz, 2H), 2.40 – 2.30 (m, 6H), 1.80 (s, 6H), 1.14 (t, J = 7.2 Hz, 3H).
170	549.95	(DMSO-d_6): δ 10.86 (bs, 1H), 9.61 (bs, 2H), 9.36 (s, 2H), 8.84 (s, 1H), 8.53 (d, J = 7.8 Hz, 1H), 8.40 (s, 1H), 8.16 (s, 1H), 8.04 (t, J = 7.2 Hz, 1H), 7.49 (s, 1H), 7.22 (s, 1H), 3.91 (s, 2H), 3.22 (bs, 2H), 1.86 (s, 6H), 1.13 (t, J = 6.9 Hz, 3H).

171	549.93	HCl salt - (DMSO-d_6): δ 10.83 (bs, 1H), 9.33 (s, 2H), 8.84 (s, 1H), 8.53 (d, J = 7.7 Hz, 1H), 8.46 (s, 3H), 8.39 (s, 1H), 8.15 (s, 1H), 8.03 (t, J = 6.9 Hz, 1H), 7.48 (s, 1H), 7.18 (s, 1H), 4.20 (s, 1H), 3.22 (s, 2H), 3.01 (qd, J = 17.5, 5.3 Hz, 2H), 1.81 (d, J = 7.2 Hz, 6H), 1.13 (t, J = 6.1 Hz, 3H).(COOH signal obscured by H_2O)
172	519.97	HCl salt - (DMSO-d_6): δ 10.88 (bs, 1H), 9.34 (s, 2H), 8.85 (dd, J = 4.8, 0.8 Hz, 1H), 8.58 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.07–7.90 (m, 4H), 7.53–7.46 (m, 1H), 7.20 (bs, 1H), 3.23 (dd, J = 6.8, 4.9 Hz, 2H), 2.87 (dd, J = 14.8, 6.0 Hz, 2H), 2.48 (d, J = 7.4 Hz, 2H), 1.86–1.79 (m, 8H), 1.14 (t, J = 7.2 Hz, 3H).
173	525.15	(DMSO-d_6): δ 10.62 (br s, 1H), 9.40 (s, 2H), 8.86 – 8.80 (m, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 1.5 Hz, 1H), 8.17 (d, J = 1.2 Hz, 1H), 8.02 (td, J = 7.8, 1.8 Hz, 1H), 7.47 (dd, J = 7.1, 5.2 Hz, 1H), 6.91 – 6.81 (m, 1H), 5.81 (s, 1H), 3.43 – 3.33 (m, 2H), 3.26 – 3.17 (m, 2H), 3.17 – 3.05 (m, 2H), 2.64 (t, J = 11.5 Hz, 2H), 2.39 – 2.21 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H)
174	476.07	(DMSO-d_6): δ 10.61 (br s, 1H), 9.41 (s, 2H), 8.85 – 8.82 (m, 1H), 8.54 – 8.50 (m, 2H), 8.41 (d, J = 1.5 Hz, 1H), 8.39 – 8.29 (m, 1H), 8.18 (d, J = 1.5 Hz, 1H), 8.05 – 8.00 (m, 1H), 7.50 – 7.45 (m, 1H), 6.90 – 6.84 (m, 1H), 5.70 (s, 1H), 3.28 – 3.14 (m, 6H), 2.41 – 2.29 (m, 2H), 2.12 – 2.00 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H).
175	548.25	(DMSO-d_6) δ 10.62 (br s, 1H), 9.33 (s, 2H), 8.73 (d, J= 4.40 Hz, 1H), 8.39 (m, 2H), 8.13 (s, 1H), 7.36 (d, J= 4.0 Hz, 1H), 6.86 (m, 1H), 5.16 (s, 1H), 4.08 (m, 1H), 3.74 (s, 2H), 3.58 (m, 2H), 3.35 (m, 2H), 3.19-3.23 (m, 2H), 2.93 (m, 2H), 1.57 (s, 6H) and 1.06-1.13 (m, 6H)
176	388.14	(DMSO-d_6) δ 10.62 (br s, 1H), 8.95 (s, 2H), 7.73 (s, 1H), 7.69 (s, 1H), 6.68 (m, 1H), 5.09 (s, 1H), 3.84 (s, 3H), 3.15-3.22 (m, 2H), 1.54 (s, 6H) and 1.09 (t, J= 7.20 Hz, 3H)
177	376.11	(DMSO-d_6) δ 10.80 (br s, 1H), 9.04 (s, 2H), 7.89-8.01 (m, 2H), 6.71 (m, 1H), 5.14 (s, 1H), 3.16-3.22 (m, 2H), 1.54 (s, 6H) and 1.09 (t, J= 7.20 Hz, 3H)
178	469.08	(DMSO/Acetone) δ 9.20 (s, 2H), 8.54 (d, J = 5.5 Hz, 1H), 8.48 (s, 1H), 8.14 (d, J = 1.6 Hz, 1H), 8.11 (s, 1H), 7.56 – 7.31 (m, 1H), 7.29 (t, J = 4.6 Hz, 1H), 5.30 (s, 1H), 4.90 – 4.81 (m, 1H), 4.02 (s, 3H), 3.24 – 3.14 (m, 2H), 1.47 (d, J = 6.6 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H).
179	563.98	HCl salt - (DMSO-d_6): δ 11.03 (s, 1H), 9.36 (s, 2H), 9.34 (s, 2H), 8.85 (d, J = 4.6 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.40 (d, J = 1.3 Hz, 1H), 8.16 (d, J = 1.3 Hz, 1H), 8.05 (dt, J = 8.0, 1.2 Hz, 1H), 7.50 (dd, J = 7.2, 4.6 Hz, 1H), 7.38 (s, 1H), 4.10 (s, 2H), 3.58 (s, 1H), 3.32 – 3.08 (m, 4H), 2.73 (t, J = 7.3 Hz, 2H), 1.86 (s, 6H), 1.13 (t, J = 7.3 Hz, 3H).

180	531.94	HCl salt - (DMSO-d_6): δ = 10.85 (bs, 1H), 9.40 (bs, 1H), 9.35 (s, 2H), 9.26 (bs, 1H), 8.85 (d, J = 4.1 Hz, 1H), 8.57 (d, J = 8.2 Hz, 1H), 8.42 (d, J = 1.4 Hz, 1H), 8.17 (d, J = 1.4 Hz, 1H), 8.03 (dd, J = 11.1, 4.4 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.15 (bs, 1H), 3.45–3.31 (m, 3H), 3.26-3.14 (m, 4H), 2.24 (q, J = 6.9 Hz, 2H), 1.82 (d, J = 16.6 Hz, 6H), 1.13 (t, J = 7.2 Hz, 3H).
181	547.97	HCl salt - (DMSO-d_6): δ 10.87 (bs, 1H), 10.02 (bs, 1H), 9.63 (bs, 1H), 9.39 (s, 2H), 8.85 (d, J = 4.2 Hz, 1H), 8.56 (d, J = 8.2 Hz, 1H), 8.42 (d, J = 1.2 Hz, 1H), 8.18 (d, J = 1.3 Hz, 1H), 8.05 (t, J = 7.7 Hz, 1H), 7.49 (dd, J = 7.1, 5.0 Hz, 1H), 7.19 (bs, 1H), 4.46 (s, 2H), 4.01–3.88 (m, 2H), 3.76 (t, J = 9.8 Hz, 1H), 3.24 (dd, J = 17.6, 11.7 Hz, 3H), 3.15 (bs, 1H), 1.87 (d, J = 32.2 Hz, 6H), 1.13 (t, J = 7.2 Hz, 3H).
182	428.19	(DMSO-d_6) δ 10.62 (br s, 1H), 9.02 (s, 2H), 7.69-7.70 (m, 2H), 6.68 (m, 1H), 5.14 (s, 1H), 3.92 (d, J= 6.80 Hz, 2H), 3.14-3.21 (m, 2H), 1.54 (s, 6H), 1.18-1.20 (m, 1H), 1.08 (t, J= 7.20 Hz, 3H), 0.50-0.55 (m, 2H) and 0.27-0.31 (m, 2H)
183	432.13	(DMSO-d_6) δ 10.63 (br s, 1H), 9.01 (s, 2H), 7.71-7.74 (m, 2H), 6.68 (m, 1H), 5.11 (s, 1H), 4.20 (t, J= 4.80 Hz, 2H), 3.64 (t, J= 4.80 Hz, 2H), 3.24 (s, 3H), 3.16-3.20 (m, 2H), 1.53 (s, 6H), and 1.09 (t, J= 7.20 Hz, 3H)
184	616	(DMSO-d_6): δ 10.96 (s, 1H), 9.78 – 9.06 (m, 2H), 9.34 (s, 2H), 8.85 (d, J = 4.5 Hz, 1H), 8.55 (d, J = 8.1 Hz, 1H), 8.41 (d, J = 1.4 Hz, 1H), 8.17 (d, J = 1.4 Hz, 1H), 8.05 (td, J = 8.1, 1.7 Hz, 1H), 7.50 (dd, J = 7.1, 4.5 Hz, 1H), 7.26 (s, 1H), 4.12 (s, 4H), 3.58 (s, 2H), 3.32 – 3.15 (m, 4H), 1.87 (s, 6H), 1.13 (t, J = 7.2 Hz, 3H).
185	536.12	(DMSO-d_6): δ 10.69 (s, 1H), 9.33 (s, 2H), 8.77 (d, J = 5.0 Hz, 1H), 8.45 – 8.33 (m, 2H), 8.14 (d, J = 1.4 Hz, 1H), 7.44 (d, J = 5.0 Hz, 1H), 7.02 – 6.89 (m, 1H), 5.30 (s, 1H), 4.90 (d, J = 5.8 Hz, 1H), 3.70 (s, 2H), 3.23 (dd, J = 13.3, 6.5 Hz, 2H), 2.70 (dd, J = 18.3, 6.0 Hz, 8H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).
186	418.2	(DMSO-d_6) δ 10.68 (br s, 1H), 9.06 (s, 2H), 7.71-7.73 (m, 2H), 6.78 (m, 1H), 5.12 (s, 1H), 4.88 (t, J= 5.20 Hz, 1H), 4.12 (t, J= 5.20 Hz, 2H), 3.70 (t, J= 4.80 Hz, 2H), 3.14-3.21 (m, 2H), 1.54 (s, 6H), and 1.08 (t, J= 7.20 Hz, 3H)
187	550.23	(DMSO-d_6) δ 10.60 (br s, 1H), 9.32 (s, 2H), 8.76 (d, J= 4.80 Hz, 1H), 8.36-8.40 (m, 2H), 8.13 (s, 1H), 7.42 (d, J= 4.40 Hz, 1H), 6.85 (m, 1H), 5.13 (s, 1H), 3.67 (s, 2H), 3.20-3.23 (m, 2H), 2.66-2.69 (m, 8H), 1.57 (s, 6H) and 1.11 (t, J= 7.20 Hz, 3H)
188	566.23	(DMSO-d_6) δ 10.62 (br s, 1H), 9.32 (s, 2H), 8.78 (d, J= 4.80 Hz, 1H), 8.44 (s, 1H), 8.37 (s, 1H), 8.13 (s, 1H), 7.45 (d, J= 4.80 Hz, 1H), 6.86 (m, 1H), 5.15 (s, 1H), 3.75 (s, 2H), 3.18-3.25 (m, 2H), 2.93 (m, 4H), 2.69-2.79 (m, 4H), 1.57 (s, 6H) and 1.11 (t, J= 7.60 Hz, 3H)

189	445.22	(DMSO-d_6) δ 10.68 (br s, 1H), 8.98 (s, 2H), 7.83 (s, 1H), 7.58 (s, 1H), 6.70 (m, 1H), 5.11 (br s, 1H), 3.18 (m, 4H), 3.07 (s, 3H), 2.89 (m, 2H), 2.54 (s, 3H), 1.53 (s, 6H), and 1.08 (t, J= 7.20 Hz, 3H)
190	514.98	(DMSO-d_6) δ 10.60 (br s, 1H), 9.39 (s, 2H), 8.85 (d, J = 4.6 Hz, 1H), 8.61 – 8.49 (m, 1H), 8.47 – 8.38 (m, 1H), 8.22 – 8.15 (m, 1H), 8.04 (t, J = 7.8 Hz, 1H), 7.49 (dd, J = 7.3, 4.9 Hz, 1H), 6.98 – 6.88 (m, 1H), 5.09 (d, J = 7.5 Hz, 2H), 3.25 – 3.21 (m, 2H), 1.88 (s 6H), 1.16 – 1.11 (m, 3H).
191	582.23	(DMSO-d_6+D_2O) δ 9.25 (s, 2H), 8.74 (d, J= 4.80 Hz, 1H), 8.35 (s, 1H), 8.30 (s, 1H), 8.06 (s, 1H), 7.45 (d, J= 5.20 Hz, 1H), 3.84 (s, 2H), 3.11-3.21 (m, 6H), 2.94 (m, 4H), 1.54 (s, 6H) and 1.07 (t, J= 7.20 Hz, 3H)
192	524.22	(DMSO-d_6) δ 10.64 (br s, 1H), 9.01 (s, 2H), 7.85 (s, 1H), 7.71 (s, 1H), 6.98 (s, 1H), 6.90 (m, 2H), 6.69 (m, 1H), 5.08-5.10 (m, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.17-3.20 (m, 2H), 1.51 (s, 6H), and 1.09 (t, J= 7.20 Hz, 3H)
193	444.16	(DMSO-d_6) δ 10.62 (br s, 1H), 8.99 (s, 2H), 7.72 (s, 1H), 7.70 (s, 1H), 6.68 (m, 1H), 5.27 (d, J= 5.20 Hz, 1H), 4.82 (m, 1H), 3.99-4.13 (m, 3H), 3.63-3.70 (m, 2H), 3.16-3.20 (m, 2H), 1.90-1.96 (m, 1H), 1.64-1.80 (m, 2H), 1.59-1.64 (m, 1H), 1.46 (d, J= 6.80 Hz, 3H) and 1.09 (t, J= 7.20 Hz, 3H)
194	429.24	(DMSO-d_6) δ 10.68 (br s, 1H), 9.05 (s, 2H), 7.79 (s, 1H), 7.61 (s, 1H), 6.70 (m, 1H), 5.27 (d, J= 5.60 Hz, 1H), 4.82 (m, 1H), 3.48 (m, 4H), 3.16-3.19 (m, 2H), 2.73 (m, 4H), 1.45 (d, J= 6.40 Hz, 3H) and 1.08 (t, J= 7.20 Hz, 3H)
195	442.31	(DMSO-d_6) δ 9.11 (s, 2H), 7.69 (m, 1H), 7.30 (s, 1H), 7.05 (m, 1H), 6.57 (m, 1H), 5.14 (s, 1H), 3.19 (m, 5H), 1.98-2.01 (m, 2H), 1.53 (s, 6H), 1.27-1.35 (m, 4H) and 1.08 (m, 3H)
196	508.09	(DMSO-d_6): δ 9.32 (s, 2H), 8.75 (d, J = 5.0 Hz, 1H), 8.47 (s, 1H), 8.36 (d, J = 1.5 Hz, 1H), 8.20 (s, 1H), 8.13 (d, J = 1.5 Hz, 1H), 7.45 (d, J = 5.0 Hz, 1H), 6.99 (t, J = 5.5 Hz, 1H), 3.94 (s, 3H), 3.53 (t, J = 5.7 Hz, 2H), 3.21 (tt, J = 13.0, 6.5 Hz, 2H), 2.68 (t, J = 5.7 Hz, 2H), 2.54 (s, 1H), 1.57 (s, 6H), 1.12 (t, J = 7.2 Hz, 3H).
197	420	(CD_3OD) δ 8.80 (d, J = 5.2 Hz, 2H), 8.56 (s, 1H), 8.15 - 8.11 (m, 2H), 8.04 (s, 1H), 7.94 - 7.88 (m, 2H), 7.43 (s, 2H), 7.35 (t, J = 7.2 Hz, 1H), 5.03 (q, J = 6.0 Hz, 1H), 3.42 - 3.38 (m, 2H), 1.60 (d, J = 6.4 Hz, 3 H), 1.26 (t, J = 7.2 Hz, 3H).
198	542.3	(DMSO-d_6): δ 10.61 (s, 1H), 9.33 (s, 2H), 8.76 (d, J = 5.2 Hz, 1H), 8.42 (s, 1H), 8.37 (d, J = 1.3 Hz, 1H), 8.13 (d, J = 0.7 Hz, 1H), 7.44 (dd, J = 5.0, 1.1 Hz, 1H), 6.88 (t, J = 5.1 Hz, 1H), 5.75 (s, 1H), 5.13 (s, 1H), 3.64 (s, 2H), 3.26 – 3.17 (m, 2H), 1.57 (s, 6H), 1.12 (t, J = 7.2 Hz, 3H).

199	487.21	(DMSO-d_6) δ 10.63 (br s, 1H), 9.04 (s, 2H), 7.75 (s, 1H), 7.70 (s, 1H), 6.68 (m, 1H), 5.10 (s, 1H), 4.17 (t, J= 5.20 Hz, 2H), 3.53 (m, 4H), 3.15-3.21 (m, 2H), 2.64 (t, J= 5.20 Hz, 2H), 2.37 (m, 4H), 1.53 (s, 6H) and 1.08 (t, J= 7.20 Hz, 3H)
200	448.14	(DMSO-d_6) δ 10.84 (br s, 1H), 8.93 (s, 2H), 7.63-7.69 (m, 2H), 6.72 (m, 1H), 5.21 (br s, 1H), 3.37 (t, J= 6.40 Hz, 2H), 3.11-3.15 (m, 5H), 2.98 (t, J= 6.40 Hz, 2H), 1.58 (s, 6H), and 1.04 (t, J= 6.80 Hz, 3H)
201	464.14	(DMSO-d_6) δ 11.06 (br s, 1H), 9.03 (s, 2H), 7.92-7.98 (m, 2H), 6.79 (m, 1H), 5.27 (br s, 1H), 3.65 (m, 1H), 3.45 (m, 1H), 3.02-3.15 (m, 6H), 2.85-2.89 (m, 1H), 1.57 (s, 6H), and 1.05 (t, J= 7.20 Hz, 3H)
202	451.21	(DMSO-d_6): δ 10.59 (s, 1H), 9.33 (s, 2H), 8.63 (d, J = 6 Hz, 1H), 8.38 (d, J = 0.8 Hz, 1H), 8.12 (s, 1H), 8.02 (d, J = 1.2 Hz, 1H), 7.05 (dd, J = 5.6, 2 Hz, 1H), 6.87 (br t, J = 5.2 Hz, 1H), 5.30 (d, J = 5.2 Hz, 1H), 4.88 (p, J = 6 Hz, 1H), 3.99 (s, 3H), 3.21 (p, J = 6.4 Hz, 2H), 1.49 (d, J = 6.4 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).

[a] Compound **149** was prepared by coupling **Precursor 81** with **Intermediate 1** under Suzuki coupling conditions as previously described then was subsequently converted to the target compound as follows. Zinc (177 mg) was added to a solution of 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl bis(2,2,2-trichloroethyl) phosphate (230 mg) in a mixture of pyridine (1.5 mL) and acetic acid (0.3 mL) and the mixture stirred at RT for 2 h. The mixture was filtered through celite, washing with pyridine (3 x 10 mL) and concentrated *in vacuo*. The residue was treated with MeOH (30 mL) to give a solid, which was collected by filtration. This was purified by reverse phase chromatography eluting with 0-100% ACN/ H_2O, followed by 50% MeOH/H_2O 50% ammonia) to give Compound **149** as the *bis* ammonium salt (50 mg).

ADME Assays

The following assay(s) may be used to assess the properties of a prodrug and the potential suitability of the prodrug to deliver a compound *in vivo*.

Chemical Stability Assay

Compounds may be tested for chemical stability across four pH values i.e. 2.1, 4.5, 7.4 and 9.1 and in water. Stress solutions are prepared with 10% acetonitrile and samples introduced from DMSO stocks (2mM) to give a final concentration of 16μM. Test samples are analysed by HPLC using a C8 reverse phase column (Phenomenex Kinetex™ 2.6 μm C8 100 Å LC Column 50 x 3 mm or similar) with an elution

gradient of 5-100% acetonitrile:water + 0.1% formic acid. The assay is conducted over 24hrs with 2-hourly injections. Data analysis is performed using peak areas at 254nm and LCMS for mass determination.

In an alternative method, compounds are dissolved in DMSO are diluted to produce triplicate 10 μM solutions in HEPES pH 7.4 containing 5% DMSO. The samples are incubated for 24 h at 37°C and analysed by LCMS following the addition of 2 volumes of methanol. The percentage of compound remaining is determined by comparing peak areas to a T0 sample.

The chemical stability of representative Compounds **19, 123, 133** and **134** were tested and determined to be chemically stable at pH 7.4 with ≥95% of the compound remaining at 24 hours.

Thermodynamic Solubility

In a 1.5 mL eppendorf tube, approximately 2 mg of compound is resuspended in a volume of HEPES buffer pH 7.4 to achieve a 5 mg/mL suspension. The tubes are placed on an orbital shaker at room temperature and following shaking for 24 hours the tubes are spun at 1400 rpm in a bench top centrifuge to pellet the undissolved compound. Duplicate 150 μL aliquots of the supernatant are then transferred into two ultracentrifuge tubes and spun at 357440 g for 4 hours at 20°C. 50 μL of the supernatant from each tube is then diluted with 100 μL of methanol and analysed by HPLC or LCMS to determine the concentration of compound in solution by comparing to a standard curve. The thermodynamic solubility of representative Compounds **19**, **123**, **134** and **153** were tested and determined to be highly soluble, at ≥2mg/mL, at pH 7.4.

Microsomal Stability

In a 96 well polypropylene plate, 10 μM compound is prepared in 100 mM KPO_4 buffer pH 7.4, 5 mM $MgCl_2$, 25 μg/ml Alamethicin, 1 mg/ml (protein) liver microsomes (mouse) and a final DMSO concentration of 0.1% in 100 μl in duplicate. The plate is pre-incubated at 37°C for 10 minutes after which reactions are initiated by the addition of NADPH and UDPGA to a final concentration of 1 mM and 5 mM respectively. Reactions are incubated at 37°C and terminated by the addition of 100 μl DMSO at 0, 10, 30 and 60 minutes. Samples of 100 μl are withdrawn and added to 50 μl ice cold methanol and mixed on an orbital shaker for 10 minutes to precipitate the proteins. The samples are then centrifuged at 4000 rpm and 10°C for 30 minutes and supernatants are analysed by LCMS. The T1/2 and clearance are determined by

linear regression from the peak areas. The microsomal stability of representative Compounds **19, 123, 133** and **134** were tested and determined to be unstable, in each case the major metabolite being the parent alcohol, with a half-life less than 20 mins.

Plasma Stability

Compounds dissolved in DMSO are diluted to produce duplicate 50 µl aliquots of 10 µM solutions in neat plasma containing 1% DMSO in 96 well polypropylene plates. Following incubation at 37°C for 5 hours, 100 µl ice cold acetonitrile is added to the samples and mixed on an orbital shaker for 10 minutes to precipitate the proteins. The samples are then centrifuged at 4000 rpm and 10°C for 30 minutes and supernatants are analysed by LCMS. The recovery and percentage of compound remaining is determined by comparing peak areas to a DMSO stock and T0 sample respectively.

Biological Data

The *in vitro* and *in vivo* antiviral activity of the compounds of the invention may be determined using the following protocols.

On-Target Enzyme Assay: Determination of Gyrase ATPase Activity

Gyrase converts ATP into ADP and inorganic phosphate. The released phosphate can be detected by the addition of malachite green solution and measured by monitoring the increase in absorbance at 600 nm. The ATPase assay is carried out in a buffer containing 2 mU/µL Gyrase enzyme (A_2B_2 complex from *Staphylococcus aureus*), 0.08 mg/mL double-stranded DNA, 8 mM HEPES.KOH pH 7.6, 100 mM K glutamate, 2 mM Mg acetate, 2 mM DTT, 0.01 mg/mL BSA, and 5% DMSO solution containing the inhibitor. Alternatively, the ATPase assay is carried out in a buffer containing 4.8 µg/mL Gyrase enzyme (A_2B_2 complex from *Escherichia coli*), 0.08 µg/mL ssDNA, 35 mM Tris pH 7.5, 24 mM KCl, 2 mM $MgCl_2$, 6.5% Glycerol, 2 mM DTT, 1.8 mM Spermidine, 0.5 mg/mL BSA and 5% DMSO solution containing the inhibitor. The reaction is started by adding ATP to a final concentration of 1 mM and allowed to incubate at 30°C for 60 minutes. The reaction is stopped by adding 200 µL of malachite green solution (0.034% malachite green, 10 mM ammonium molybdate, 1 M HCl, 3.4% ethanol, 0.01% tween 20). Colour is allowed to develop for 5 minutes and the absorbance at 600 nm is measured spectrophotometrically. The IC_{50} values are determined from the absorbance readings using no compound and no enzyme controls.

The compounds of the invention demonstrated on target enzyme activity with the majority of compounds tested showing Gyrase ATPase activity IC_{50} values less than 1 µg/mL, with most of these being less than 0.1 µg/mL.

Bacterial Assay: Determination of Antibacterial Activity

Compounds of the invention were tested for antimicrobial activity by susceptibility testing in liquid or on solid media. MICs for compounds against each strain were determined by the broth microdilution or agar dilution method according to the guidelines of the Clinical Laboratories and Standards Institute, formerly the National Committee for Clinical Laboratory Standards (Clinical Laboratories and Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*; *Approved Standard–Seventh Edition*. Document M7-A7. CLSI, Wayne, Pa, 2006; Clinical Laboratories and Standards Institute. The Gram positive bacterial strains tested include *S. aureus* (*Staphylococcus aureus* (Isolate ID ATCC 29213)), *S. epidermidis* (*Staphylococcus epidermidis* (Isolate ID ATCC 12228)), *E. faecalis* (*Enterococcus faecalis* (Isolate ID ATCC 29212)), *E. faecium* (*Enterococcus faecium* (Isolate ID ATCC 700221)), *S. pyogenes* (*Streptococcus pyogenes* (Isolate ID ATCC 51339)) and *S. pneumoniae* (*Streptococcus pneumoniae* (Isolate ID ATCC 49619)). The Gram negative bacterial strains tested include *H. influenzae* (*Haemophilus influenzae* (Isolate ID ATCC 49247)), *A. baumannii* (*Acinetobacter baumannii* (Isolate ID ATCC 19606)), *E. coli* (*Escherichia coli* (Isolate ID ATCC 25922)), *K. pneumoniae* (*Klebsiella pneumoniae* (Isolate ID ATCC 13882)), *L. pneumophila* (*Legionella pneumophila* (Isolate ID ATCC 33152)), *M. catarrhalis* (*Moraxella catarrhalis* (Isolate ID ATCC 25240)) and *N. gonorrhoeae* (*Neisseria gonorrhoeae* (Isolate ID ATCC 49226)).

Gram Positive Antibacterial Activity

Representative compounds of the invention were tested for activity against one or more Gram positive bacterial strains and the results are presented in Tables 1 and 2.

Table 1. *S.aureus* (ATCC 29213) *minimal inhibitory concentration (MIC)*

MIC (µg/mL)	Representative compound example number
≤1	1, 2, 3, 4, 6, 7, 8, 10, 12, 13, 14, 15, 17, 18, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 48, 49, 50, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 67, 68, 69, 70, 71, 73, 74, 75, 76, 77, 78, 80,

	81, 82, 83, 84, 87, 88, 92, 93, 94, 95, 96, 98, 100, 101, 104, 106, 107, 108, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 125, 127, 128, 130, 131, 154, 155, 156, 157, 158, 162, 164, 168, 173, 175, 176, 177, 178, 182, 183, 185, 187, 188, 191, 192, 193, 197, 198, 202
2	16, 20, 45, 52, 65, 66, 79, 85, 91, 99, 103, 109, 110, 150, 151, 159, 196, 199
4	11, 21, 46, 51, 97, 186
8	9, 47, 72, 86, 89, 174
16	5, 41, 44, 90, 102, 105, 117, 194

Table 2. *S.pyogenes* (ATCC 51339) *minimal inhibitory concentration (MIC)*

MIC (µg/mL)	**Representative compound example number**
≤1	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 45, 48, 49, 50, 51, 52, 53, 54, 55, 56, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 74, 75, 76, 77, 78, 80, 81, 82, 83, 84, 85, 86, 87, 88, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 125, 127, 128, 130, 131, 154, 155, 156, 157, 158, 159, 162, 164, 168, 173, 175, 176, 178, 182, 183, 185, 187, 188, 191, 192, 197
2	13, 57, 79, 89, 90, 151, 174, 177, 186, 193, 199
4	46
8	47, 72, 150, 163
16	41, 44, 102

Gram Negative Antibacterial Activity

Selected compounds of the invention were also tested for activity against the Gram negative bacterial strain *H.influenzae* (ATCC 49247) and the results are presented in Table 3.

Table 3. *H.influenzae* (ATCC 49247) *minimal inhibitory concentration (MIC)*

MIC (µg/mL)	**Representative compound example number**

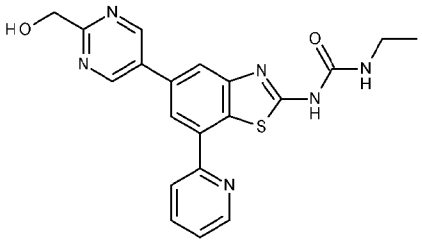
≤2	1, 6, 7, 8, 10, 15, 17, 22, 23, 27, 28, 30, 31, 32, 35, 36, 38, 39, 40, 43, 53, 55, 56, 58, 59, 61, 62, 63, 64, 68, 69, 70, 71, 73, 74, 75, 76, 80, 81, 82, 83, 87, 88, 92, 95, 96, 99, 100, 104, 111, 113, 114, 115, 116, 118, 119, 121, 122, 125, 127, 130, 131, 154, 155, 157, 158, 168, 173, 175, 178, 185, 187, 198, 202

Pharmacokinetic Assays: Determination of PK Profile

The pharmacokinetic profiles of compounds are determined by measuring the compound concentration in plasma by LC/MS/MS following a single intravenous or peroral administration of the compounds at a dose of 1 or 3 mg/kg individually or in a cassette of up to 5 compounds. The concentrations are described as the mean plasma concentrations at each time point from three animals. Intravenous dose formulation is administered as a single bolus dose through the tail vein. Oral dose formulation is administered to animals by an oral gavage needle. In both cases the dose volume is 5.0 mL/kg. Blood is collected from rats using a jugular vein catheter and from anesthetized mice through a capillary guided into the retro-orbital plexus. The collected blood is then centrifuged to obtain plasma and the compounds extracted into methanol prior to determining the compound concentration by LC/MS/MS.

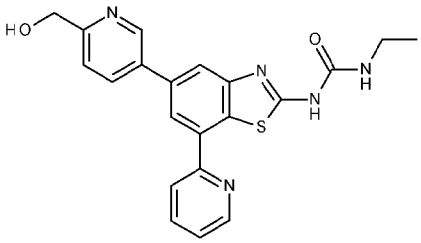
The pharmacokinetic profiles of selected compounds of the invention were compared directly with their primary alcohol analogues, Compounds A and B below, in the rat assay (IV).

1-Ethyl-3-[5-[2-(hydroxymethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea (**Compound A**)



MS: 406.99 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 9.34 (s, 2H), 8.84 (d, J = 4.1 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.40 (d, J = 1.1 Hz, 1H), 8.16 (s, 1H), 8.03 (td, J = 8.0, 1.6 Hz, 1H), 7.48 (dd, J = 7.0, 5.0 Hz, 1H), 6.91 (s, 1H), 5.39 (t, J = 6.1 Hz, 1H), 4.72 (d, J = 5.9 Hz, 2H), 3.26 – 3.21 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H).

1-Ethyl-3-[5-[6-(hydroxymethyl)-3-pyridyl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea (**Compound B**)



MS: 406.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): d 10.62 (br s, 1H), 9.0 (d, J= 2.0 Hz, 1H), 8.82 (d, J= 4.40 Hz, 1H), 8.50 (d, J= 8.0 Hz, 1H), 8.30-8.32 (m, 2H), 7.98-8.03 (m, 2H), 7.60 (d, J= 8.40 Hz, 1H), 7.44-7.47 (m, 1H), 6.87 (m, 1H), 5.49 (t, J= 5.60 Hz, 1H), 4.65 (d, J= 5.60 Hz, 2H).

The results are shown in Table 4 and presented graphically in Figures 1A and 1B where the X axis denotes time (hours) and the Y axis denotes plasma concentration (µg/mL). The AUC_{iv}, clearance and $T_{1/2}$ values are provided in the following table where AUC_{iv} is area under the curve for intravenous (IV) and $T_{1/2}$ represents the compound half-life. Surprisingly, the compounds of the invention demonstrated improved clearance and an increase in AUC_{iv} and half-life when compared with Compounds A and B.

Table 4: *AUC_{iv}, clearance and half-life values for selected compounds compared against their primary alcohol substituted analogue compounds A and B in the rat assay.*

Cpd No.	**Dose (mg/kg)**	**AUC_{iv} (µg.hr/mL)**	**Clearance (mL.min/kg)**	**$T_{1/2}$ (min)**
A	3	2	25	81
B	3	1.8	28	60
1	1	3.1	4.3	203
17	3	4	12	107
27	1	1.13	13	158

Animal Models of Infection

Suitable models of infection will be familiar to those skilled in the art and include the following suitable for intravenous (IV) or oral (PO) dosing.

Thigh Infection Model(s)

Mouse: The thighs of female CD-1 mice (18-22 g), rendered neutropenic by the intraperitoneal administration of cyclophosphamide (150 mg/kg at day -4 and 100 mg/kg at day -1), were inoculated with approximately $2x10^5$ cfus of *S. aureus* Smith prepared from a fresh overnight culture. Compounds were administered as indicated 2 hours later and the cfus enumerated at various times post dosing by harvesting the thighs, homogenising in saline on ice and plating serial dilutions onto charcoal containing plates for growth overnight and colony counting. For example, when

dosed IV at 30 mg/kg Compounds **1** and **17** demonstrated a ≥ 3 log drop in colony forming units compared to the control. Similarly, when dosed PO at 100 mg/kg Compound **1** demonstrated a ≥ 3 log drop in colony forming units compared to the control.

Rat: The thighs of Sprague-Dawley rats (250-275 g), rendered neutropenic by the intraperitoneal administration of cyclophosphamide (75 mg/kg on days -4 and -1), were inoculated with approximately $1x10^7$ cfus of *S. aureus* ATCC29213. Compounds were administered as indicated 2 hours later and the cfus enumerated at various times post dosing by harvesting the thighs, homogenising in PBS on ice and plating serial dilutions onto CLED agar plates for growth at 37°C and colony counting. For example, when dosed IV at ≤ 40 mg/kg Compound **1** demonstrated a ≥ 3 log drop in colony forming units compared to the control.

Lung Infection Model(s)

Mouse (Gram positive): Anaesthetised female CD-1 mice (18-22 g) were inoculated intranasally with approximately 10^6 cfus of *S. pneumoniae* ATCC6301 prepared from a fresh overnight culture by placing 50 µl of inoculum on the nares and allowing the mice to inhale. Compounds were administered as indicated at 24 hours post inoculation and the cfus enumerated at 48 hours post inoculation by harvesting the lungs, homogenising in PBS on ice and plating serial dilutions onto TSA+5% blood plates for growth overnight at 37°C and colony counting. For example, when dosed IV at 30 mg/kg Compound **1** demonstrated a ≥ 3 log drop in colony forming units compared to the control.

Rat (Gram negative): Anaesthetised Sprague-Dawley rats (180-200 g), rendered neutropenic by the intraperitoneal administration of cyclophosphamide, were inoculated intratracheally with approximately $5x10^7$ cfus of *H. influenzae* prepared from a fresh culture by delivering 0.5 ml of inoculum in molten agar. Compounds were administered as indicated at 5 hours post inoculation followed by additional daily treatments and the cfus enumerated at 96 hours post inoculation by harvesting the lungs, homogenising in PBS on ice and plating serial dilutions onto bacterial growth medium for cfu determination.

Mouse survival model: Anaesthetised female CD-1 mice (18-22 g) were inoculated intranasally with approximately 10^6 cfus of *S. pneumoniae* ATCC6301 prepared from a fresh overnight culture by placing 50 µl of inoculum on the nares and allowing the mice to inhale. Compounds are administered as indicated at 24, 48 and 72 hours post

inoculation and the mice monitored for survival for seven or nine days after infection. For example, Compound **1** was dosed IV at 10 mg/kg and the results are shown in Figure 2. Compound **1** demonstrated improved efficacy with 80% of mice surviving at seven or nine days. In comparison, mice dosed with 10 mg/kg Linezolid were dead by day six. Similarly, when Compound **17** was dosed IV at 30 mg/kg 90% of mice survived at day seven.

Skin Infection Model(s)

Mouse: An area of the skin was stripped from the back dorsal surface of anaesthetised female CD-1 mice (18-22 g) by abrading with a fine emery board following removal of the fur by shaving. An infection was initiated by placing 5 µl of inoculum, containing approximately 10^7 cfus of *S. aureus* Smith prepared from a fresh overnight culture, onto the damaged skin. Compounds were administered as indicated at 4, 20, 28, 44, 52, 68 and 76 hours post inoculation and the cfus enumerated after 5 days post inoculation by harvesting the wounds, homogenising in PBS on ice and plating serial dilutions onto charcoal containing plates for growth overnight and colony counting.

Septicaemia Infection Model(s)

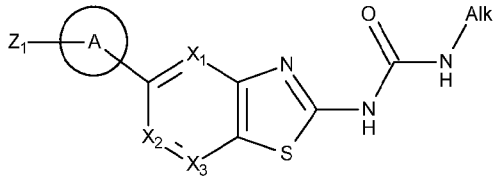
Mouse: Female CD-1 mice (18-22 g) were inoculated intraperitoneally with approximately $5x10^5$ cfus of *S. aureus* Smith prepared from a fresh overnight culture suspended in 5% hog gastric mucin. Compounds were administered as indicated at 2 hours post inoculation and the mice monitored for survival for five days after infection.

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

The reference in this specification to any prior publication, or information derived from it, or to any matter which is known, is not, and should not be taken as an acknowledgement or admission or any form of suggestion that that prior publication, or information derived from it, or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

CLAIMS

1. A compound of Formula (I)

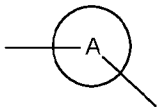


(I)

salts, racemates, diastereomers, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof

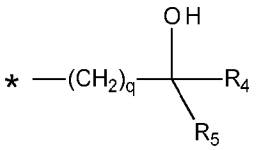
wherein

X_1 is N or C-R_1 where R_1 is selected from H, OH, optionally substituted C_{1-3}alkyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{1-3}alkoxyl, halo, haloC_{1-3}alkyl, NH_2, optionally substituted NHC_{1-3}alkyl, optionally substituted $N(C_{1-3}alkyl)_2$, optionally substituted SC_{1-3}alkyl and CN;



represents Ring A which is selected from saturated or unsaturated monocyclic C_{3-7}cycloalkyl, saturated or unsaturated monocyclic 3-7 membered heterocycle, saturated or unsaturated fused bicyclic C_{8-10}cycloalkyl, saturated or unsaturated fused bicyclic 8-10 membered-heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl and may be optionally substituted;

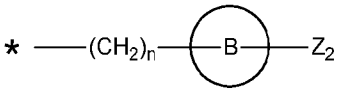
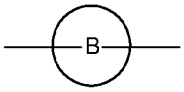
Z_1 is a secondary or tertiary alcohol of general formula



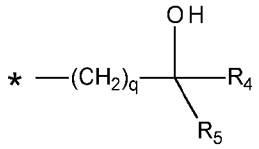
an ester, carbamate, phosphate, sulfate or prodrug thereof as defined below or Z_1 is selected from H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-6}$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl, CN and optionally substituted $(CH_2)_mNR^aR^b$ where each R^a and R^b is independently selected from H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and optionally substituted 4-6-membered heterocycle or R^a and R^b join together to form an

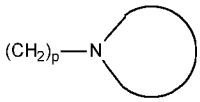
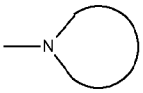
optionally substituted 4-6-membered heterocyclyl where each m is an integer independently selected from 0, 1, 2 and 3;

X_2 is N or C-R_2 where R_2 is selected from H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-6}$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl, optionally substituted $(CH_2)_mO(CH_2)_mC_{3-7}$cycloalkyl, optionally substituted $(CH_2)_mC_{3-7}$cycloalkyl, optionally substituted $(CH_2)_mO(CH_2)_m$phenyl, optionally substituted $(CH_2)_m$phenyl, optionally substituted $(CH_2)_mO(CH_2)_m$-5-10-membered heterocycle, optionally substituted $(CH_2)_m$-5-10-membered heterocycle, halo, optionally substituted haloC_{1-3}alkyl, CN, and optionally substituted $(CH_2)_mNR^aR^b$;

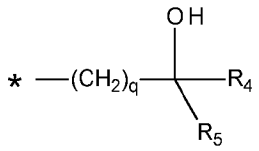
X_3 is N or C-R_3 where R_3 is selected from H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-6}$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl, optionally substituted $(CH_2)_mO(CH_2)_mC_{3-7}$cycloalkyl, optionally substituted $(CH_2)_mC_{3-7}$cycloalkyl, optionally substituted $(CH_2)_mO(CH_2)_m$phenyl, optionally substituted $(CH_2)_m$phenyl, optionally substituted $(CH_2)_mO(CH_2)_m$-5-10-membered heterocycle, optionally substituted $(CH_2)_m$-5-10-membered heterocycle, halo, haloC_{1-3}alkyl, CN and optionally substituted $(CH_2)_mNR^aR^b$ or R_3 is a group of formula  where * represents the point of attachment to the carbon ring atom; n is an integer selected from 0, 1, 2 and 3;  represents Ring B which is selected from saturated or unsaturated monocyclic C_{3-7}cycloalkyl, saturated or unsaturated monocyclic 3-7 membered heterocycle, saturated or unsaturated fused bicyclic C_{8-10}cycloalkyl, saturated or unsaturated fused bicyclic 8-10 membered-heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl and may be optionally substituted; and

Z_2 is a secondary or tertiary alcohol of general formula



an ester, carbamate, phosphate, sulfate or prodrug thereof as defined below or Z_2 is selected from H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-6}$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl, CN, optionally substituted $(CH_2)_mNR^aR^b$, optionally substituted $(CH_2)_p$-4-6-membered heterocycylic ring, optionally substituted $(CH_2)_p$-spiro-bicyclic-7-11-membered heterocycylic ring and optionally substituted  where p is an integer selected from 0, 1, 2 and 3 and  represents an optionally substituted 4-6 membered heterocyclic ring or an optionally substituted spiro bicyclic 7-11- membered heterocyclic ring; and

Alk is optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl; and with the proviso that Z_1 or Z_2 is a secondary or tertiary alcohol of general formula



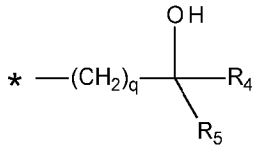
an ester, carbamate, phosphate, sulfate or prodrug thereof wherein q is an integer selected from 0, 1, 2 and 3;

R_4 is H or is selected from optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_tOC_{1-6}$alkyl, optionally substituted $(CH_2)_tOC(=O)C_{1-6}$alkyl, optionally substituted $(CH_2)_tSC_{1-6}$alkyl, optionally substituted $(CH_2)_tS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl and optionally substituted $(CH_2)_tNR^aR^b$;

R_5 is selected from optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-7}cycloalkyl ring, optionally substituted phenyl, optionally substituted 4-6-membered heterocyclyl ring, optionally substituted 5-6-membered heteroaryl ring, optionally substituted $(CH_2)_tOC_{1-6}$alkyl, optionally substituted $(CH_2)_tOC(=O)C_{1-6}$alkyl, optionally

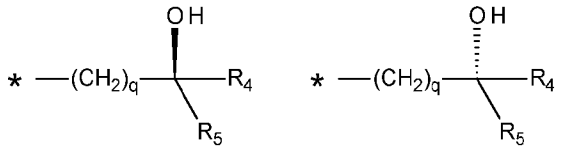
substituted $(CH_2)_tSC_{1-6}$alkyl, optionally substituted $(CH_2)_tS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl and optionally substituted $(CH_2)_mNR^aR^b$;
t is an integer selected from 1, 2, 3, 4, 5 and 6;
or R_4 and R_5 together with the carbon atom to which they are attached form an optionally substituted 4-6-membered heterocyclic ring or C_{3-7}cycloalkyl ring; and
* represents the point of attachment to Ring A or Ring B respectively; and further wherein each (CH_2) entity when present may be independently optionally substituted.

2. A compound according to claim 1 wherein Z_1 is a secondary or tertiary alcohol of general formula



or an ester, carbamate, phosphate, sulfate or prodrug thereof wherein q, R_4, R_5 and * are as defined in claim 1.

3. A compound according to claim 1 or claim 2 wherein Z_1 is a chiral alcohol of general formula



or

or an ester, carbamate, phosphate, sulfate or prodrug thereof wherein q, R_4, R_5 and * are as defined in claim 1 provided that R_4 and R_5 are different.

4. A compound according to any one of claims 1 to 3 wherein X_1 is C-R_1, X_2 is C-R_2 and X_3 is C-R_3.

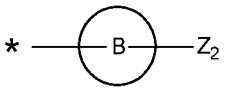
5. A compound according to any one of claims 1 to 4 wherein ring A is an optionally substituted 5-6-membered heteroaryl.

6. A compound according to any one of claims 1 to 5 wherein X_1 is C-R_1 and R_1 is H or halo.

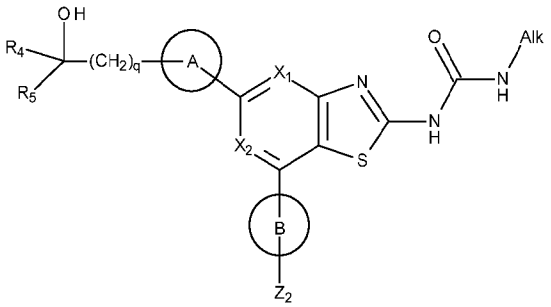
7. A compound according to any one of claims 1 to 6 wherein X_2 is C-R_2 where R_2 is selected from H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted OC_{1-6}alkyl, optionally substituted SC_{1-6}alkyl, optionally substituted $S(=O)C_{1-6}$alkyl, an optionally substituted 5-6-membered heterocycle, halo, haloC_{1-3}alkyl, CN and optionally substituted $(CH_2)_mNR^aR^b$.

8. A compound according to any one of claims 1 to 7 wherein X_3 is C-R_3 and R_3 is H.

9. A compound according to any one of claims 1 to 7 wherein X_3 is C-R_3 and R_3 is selected from optionally substituted C_{1-3}alkyl, optionally substituted OC_{1-3}alkyl, optionally substituted $(CH_2)_mNH_2$, optionally substituted $(CH_2)_mNHC_{1-3}$alkyl and optionally substituted $(CH_2)_mN(C_{1-3}alkyl)_2$ where m is as defined in claim 1.

10. A compound according to any one of claims 1 to 7 wherein X_3 is C-R_3 and R_3 is a group of formula  as defined in claim 1.

11. A compound according to claim 10 wherein the compound is of Formula (II):



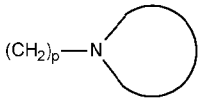
(II)

salts, racemates, diastereomers, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof

wherein X_1, X_2, Alk, Ring A, Ring B, Z_2, R_4, R_5 and q are as defined in claim 1.

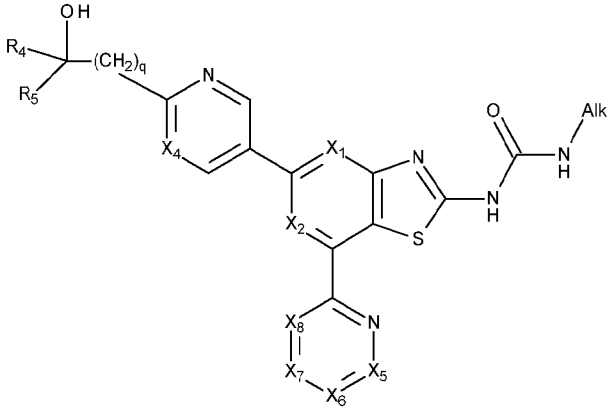
12. A compound according to any one of claims 1 to 11 wherein ring B is an optionally substituted 5-6 membered heteroaryl.

13. A compound according to any one of claims 1 to 12 wherein Z_2 is H.

14. A compound according to any one of claims 1 to 12 whererin Z_2 is selected from OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted $(CH_2)_mOC_{1-6}$alkyl, optionally substituted $(CH_2)_mSC_{1-6}$alkyl, optionally substituted $(CH_2)_mS(=O)C_{1-6}$alkyl, halo, optionally substituted haloC_{1-3}alkyl, $(CH_2)_mNH_2$, optionally substituted $(CH_2)_mNHC_{1-6}$alkyl, optionally substituted $(CH_2)_mN(C_{1-6}alkyl)_2$, optionally substituted $(CH_2)_p$-4-6-membered heterocyclic ring, optionally substituted $(CH_2)_p$-spiro-bicyclic-7-11-membered heterocyclic ring and optionally substituted 

.

15. A compound according to claim 1 wherein the compound is of general formula (III):



(III)

salts, racemates, diastereomers, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof

wherein X_1, X_2, Alk, R_4, R_5 and q are as defined in claim 1;

X_4 is N, CH, C-halo or C-C_{1-3}alkoxy;

X_5, X_6, X_7 and X_8 are each independently selected from N, C-H or C-Z_2 where Z_2 is as defined in claim 1 provided that no more than one of X_5, X_6, X_7 or X_8 is N.

16. A compound according to any one of claims 1 to 15 wherein q is 0.

17. A compound according to claim 1 selected from the group consisting of:

1) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;
2) 1-ethyl-3-[7-[4-[(3-hydroxy-3-methyl-azetidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;
3) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(tetrahydrofuran-2-ylmethoxy)-1,3-benzothiazol-2-yl]urea;
4) 1-ethyl-3-[6-fluoro-5-[6-[hydroxy(3-pyridyl)methyl]-3-pyridyl]-1,3-benzothiazol-2-yl]urea;
5) 1-(2-hydroxyethyl)-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;
6) 1-ethyl-3-[5-[5-(1-hydroxyethyl)pyrazin-2-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;
7) 1-[5-[2-[(1S*,2R*)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (mixture 1-[5-[2-[(1S,2R)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea; and 1-[5-[2-[(1R,2S)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea);
8) 1-[5-[2-[(3R*,4S*)-3,4-dihydroxytetrahydropyran-4-yl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (mixture 1-[5-[2-[(3R,4S)-3,4-dihydroxytetrahydropyran-4-yl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea; and 1-[5-[2-[(3S,4R)-3,4-dihydroxytetrahydropyran-4-yl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea);
9) 1-ethyl-3-[5-[4-(1-hydroxyethyl)triazol-1-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;
10) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-pyrimidin-2-yl-1,3-benzothiazol-2-yl]urea;
11) 1-ethyl-3-[5-[4-(1-hydroxy-1-methyl-ethyl)imidazol-1-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;
12) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-methoxy-1,3-benzothiazol-2-yl]urea;
13) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(methoxymethyl)-1,3-benzothiazol-2-yl]urea;

14) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[(6-methyl-3-pyridyl)methoxy]-1,3-benzothiazol-2-yl]urea;

15) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(methylsulfanylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

16) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(methylsulfinylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

17) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

18) 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl 4-methylpiperazine-1-carboxylate;

19) 4-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethoxy]-4-oxo-butanoic acid;

20) O4-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] O1-methyl butanedioate;

21) 4-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethoxy]-4-oxo-butanoic acid;

22) 1-ethyl-3-[5-[2-[(1R)-1-hydroxyethyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

23) 1-ethyl-3-[5-[2-[(1S)-1-hydroxyethyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

24) 1-ethyl-3-[5-[6-[hydroxy-(1-methylimidazol-2-yl)methyl]-3-pyridyl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

25) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[5-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

26) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(pyrrolidin-1-ylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

27) 1-ethyl-3-[5-[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

28) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

29) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(3-hydroxypyrrolidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

30) 1-ethyl-3-[7-[4-[(3-hydroxyazetidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

31) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(3-methoxyazetidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

32) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(2-morpholinoethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

33) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(1-morpholinoethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

34) 1-[7-[4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

35) 1-ethyl-3-[7-[4-[[(3S)-3-fluoropyrrolidin-1-yl]methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

36) 1-ethyl-3-[7-[4-[[(3R)-3-fluoropyrrolidin-1-yl]methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

37) 1-[7-[4-[(3,3-difluoro-1-piperidyl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

38) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(3-morpholinopropoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

39) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-pyrazin-2-yl-1,3-benzothiazol-2-yl]urea;

40) 1-[5-[2-(1,2-dihydroxyethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea;

41) 1-[7-(dimethylaminomethyl)-6-hydroxy-5-[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

42) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[[(3R)-3-methoxypyrrolidin-1-yl]methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

43) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(6-methylpyrimidin-4-yl)-1,3-benzothiazol-2-yl]urea;

44) 1-ethyl-3-[6-hydroxy-5-[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]-7-(morpholinomethyl)-1,3-benzothiazol-2-yl]urea;

45) 1-[6-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-3-pyridyl]-4-methyl-piperidine-4-carboxylic acid;

46) 2-[6-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-3-pyridyl]acetic acid;

47) 1-ethyl-3-[5-[2-(1-hydroxycyclohexyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

48) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)thiazol-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

49) 1-ethyl-3-[5-[5-(1-hydroxy-1-methyl-ethyl)pyrazin-2-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

50) 1-[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-4-pyridyl]-4-methyl-piperidine-4-carboxylic acid;

51) 1-[6-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-2-pyridyl]-4-methyl-piperidine-4-carboxylic acid;

52) 1-[4-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]pyrimidin-2-yl]-4-methyl-piperidine-4-carboxylic acid;

53) 1-[7-[4-[(cyclopropylamino)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

54) 4-[[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-4-pyridyl]amino]-1-methyl-cyclohexanecarboxylic acid;

55) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

56) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[5-(2-morpholinoethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

57) 1-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-propyl-urea;

58) 1-[5-[2-[cyclopropyl(hydroxy)methyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea;

59) 1-ethyl-3-[5-[2-(1-hydroxypropyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

60) 1-ethyl-3-[5-[2-(1-hydroxy-2,2-dimethyl-propyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

61) 1-ethyl-3-[5-[2-(1-hydroxybutyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea

62) [(1R)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] (2R)-2-amino-3-methyl-butanoate;

63) [(1S)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] (2R)-2-amino-3-methyl-butanoate;

64) 1-ethyl-3-[7-[4-[[(3S)-3-fluoropyrrolidin-1-yl]methyl]-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

65) 1-ethyl-3-[7-[4-[(3-hydroxyazetidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

66) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[(3-hydroxy-3-methyl-azetidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

67) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(3-hydroxy-3-methyl-pyrrolidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

68) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[(3-methylmorpholin-4-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

69) 1-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

70) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

71) 1-[7-[4-[(2,5-dimethylmorpholin-4-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

72) (2S)-1-[[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-4-pyridyl]methyl]pyrrolidine-2-carboxylic acid;

73) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(6-oxa-2-azaspiro[3.3]heptan-2-ylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

74) 1-[5-[2-(ethylcarbamoylamino)-7-[4-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-4-methyl-piperidine-4-carboxylic acid;

75) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(2-morpholinoethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

76) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[(3-methoxyazetidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

77) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[[(3R)-3-hydroxypyrrolidin-1-yl]methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

78) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(2-methoxyethylamino)pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

79) 1-ethyl-3-[7-[4-(4-ethylpiperazin-1-yl)pyrimidin-2-yl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

80) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(2-methoxyethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

81) 1-ethyl-3-[5-[2-(1-hydroxy-2-morpholino-ethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

82) 1-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-methyl-urea;

83) 1-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-methyl-urea;

84) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-[(3-hydroxy-3-methyl-pyrrolidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

85) 1-ethyl-3-[7-[4-(2-hydroxyethylamino)pyrimidin-2-yl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

86) 1-ethyl-3-[7-[4-(3-hydroxy-3-methyl-azetidin-1-yl)pyrimidin-2-yl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

87) 1-[6-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]pyrimidin-4-yl]-4-methyl-piperidine-4-carboxylic acid;

88) 1-[5-[2-(ethylcarbamoylamino)-7-[4-(1-hydroxyethyl)-2-pyridyl]-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-4-methyl-piperidine-4-carboxylic acid;

89) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 4-methylpiperazine-1-carboxylate;

90) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-(4-hydroxy-2-pyridyl)-1,3-benzothiazol-2-yl]urea;

91) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(2-morpholinoethylamino)pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

92) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(2-methoxyethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

93) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(3-methoxyazetidin-1-yl)pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

94) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-(4-morpholinopyrimidin-2-yl)-1,3-benzothiazol-2-yl]urea;

95) 1-ethyl-3-[5-[6-(1-hydroxyethyl)-3-pyridyl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

96) 1-ethyl-3-[7-(2-pyridyl)-5-[6-(2,2,2-trifluoro-1-hydroxy-ethyl)-3-pyridyl]-1,3-benzothiazol-2-yl]urea;

97) 1-[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]pyrimidin-4-yl]-4-methyl-piperidine-4-carboxylic acid;

98) 1-ethyl-3-[5-[2-(1-ethyl-1-hydroxy-propyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

99) 1-[5-[2-(ethylcarbamoylamino)-7-[5-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-4-methyl-piperidine-4-carboxylic acid;

100) 1-[7-[4-(diethoxyphosphorylmethyl)-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

101) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

102) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[6-(morpholinomethyl)pyrazin-2-yl]-1,3-benzothiazol-2-yl]urea;

103) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(2-hydroxy-2-methyl-propyl)amino]pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

104) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(tetrahydrofuran-2-ylmethoxy)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

105) 1-ethyl-3-[7-[4-(3-hydroxyazetidin-1-yl)pyrimidin-2-yl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

106) 1-ethyl-3-[7-(5-fluoro-4-morpholino-pyrimidin-2-yl)-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

107) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

108) 1-ethyl-3-[7-[4-(morpholinomethyl)-2-pyridyl]-5-[6-(2,2,2-trifluoro-1-hydroxy-ethyl)-3-pyridyl]-1,3-benzothiazol-2-yl]urea;

109) 1-[6-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]pyrimidin-4-yl]-4-methyl-piperidine-4-carboxylic acid;

110) 1-[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]-4-pyridyl]piperidine-4-carboxylic acid;

111) 1-ethyl-3-[5-[2-(4-hydroxytetrahydropyran-4-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

112) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-[4-(2-oxa-7-azaspiro[3.5]nonan-7-ylmethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

113) 1-ethyl-3-[5-[2-(3-hydroxyoxetan-3-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

114) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(3-methoxy-3-methyl-azetidin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

115) 1-ethyl-3-[5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-7-pyrimidin-2-yl-1,3-benzothiazol-2-yl]urea;

116) 1-ethyl-3-[7-[4-(2-morpholinoethoxy)-2-pyridyl]-5-[6-(2,2,2-trifluoro-1-hydroxy-ethyl)-3-pyridyl]-1,3-benzothiazol-2-yl]urea;

117) 1-[2-[2-(ethylcarbamoylamino)-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-7-yl]pyrimidin-4-yl]-4-methyl-piperidine-4-carboxylic acid;

118) 1-[5-[2-[(1R*,2R*)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (mixture 1-[5-[2-[(1R,2R)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea; and 1-[5-[2-[(1S,2S)-1,2-dihydroxypropyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea);

119) 1-ethyl-3-[5-[2-(1-hydroxycyclopentyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

120) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[5-(morpholinomethyl)pyrimidin-2-yl]-1,3-benzothiazol-2-yl]urea;

121) 1-ethyl-3-[5-[2-[(1R)-1-hydroxyethyl]pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

122) 1-ethyl-3-[5-[2-[(1S)-1-hydroxyethyl]pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

123) 4-[3-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]oxetan-3-yl]oxy-4-oxo-butanoic acid;

124) 4-[2-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-2-hydroxy-propoxy]-4-oxo-butanoic acid;

125) 1-ethyl-3-[5-[2-(4-hydroxytetrahydropyran-4-yl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

126) 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl 2-aminoacetate;

127) 1-ethyl-3-[5-[2-(4-hydroxytetrahydrothiopyran-4-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

128) 1-ethyl-3-[5-[2-(4-hydroxy-1-methyl-4-piperidyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

129) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-(2-aminoethylamino)acetate;

130) 1-[5-[2-[(1R*,2S*)-3,3-difluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea (mixture 1-[5-[2-[(1R,2S)-3,3-difluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea; and 1-[5-[2-[(1S,2R)-3,3-difluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea);

131) 1-ethyl-3-[7-(2-pyridyl)-5-[2-[(1R*,2S*)-3,3,3-trifluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea (mixture 1-ethyl-3-[7-(2-pyridyl)-5-[2-[(1R,2S)-3,3,3-trifluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea; and 1-ethyl-3-[7-(2-pyridyl)-5-[2-[(1S,2R)-3,3,3-trifluoro-1,2-dihydroxy-propyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea);

132) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] (2S)-2-aminopropanoate;

133) 4-[(1S)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethoxy]-4-oxo-butanoic acid;

134) 4-[(1R)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethoxy]-4-oxo-butanoic acid;

135) 1-[5-[2-(1,2-dihydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

136) 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl 2-amino-2-methyl-propanoate;

137) 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl 3-aminopropanoate;

138) tert-butyl 4-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-4-hydroxy-piperidine-1-carboxylate;

139) 1-ethyl-3-[5-[2-(4-hydroxy-1-oxo-thian-4-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

140) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-(dimethylamino)acetate;

141) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-morpholinoacetate;

142) 1-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-5-[2-[(1R)-1-hydroxyethyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

143) 1-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-5-[2-[(1S)-1-hydroxyethyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

144) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 5-aminopentanoate;

145) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 5-(dimethylamino)pentanoate;

146) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-aminoacetate;

147) 1-[7-[4-[(3,3-difluoroazetidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

148) 1-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-5-[2-(3-hydroxyoxetan-3-yl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

149) 1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl dihydrogen phosphate;

150) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-methoxyethylamino)-1,3-benzothiazol-2-yl]urea;

151) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-morpholino-1,3-benzothiazol-2-yl]urea;

152) [(1R)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] dihydrogen phosphate;

153) [(1S)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] dihydrogen phosphate;

154) 1-ethyl-3-[5-[2-(3-hydroxyoxetan-3-yl)pyrimidin-5-yl]-7-[4-(morpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

155) 1-ethyl-3-[7-[4-[(3-methoxyazetidin-1-yl)methyl]-2-pyridyl]-5-[6-[2,2,2-trifluoro-1-hydroxy-ethyl]-3-pyridyl]-1,3-benzothiazol-2-yl]urea;

156) 1-[7-[4-[(4,4-difluoro-1-piperidyl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

157) 1-[5-[2-[1,2-dihydroxy-1-methyl-ethyl]pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]-3-ethyl-urea;

158) 1-ethyl-3-[5-[2-[1-hydroxyethyl]pyrimidin-5-yl]-7-(5-methyl-2-pyridyl)-1,3-benzothiazol-2-yl]urea;

159) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(4-methylpiperazin-1-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

160) [(1S)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] (2S)-pyrrolidine-2-carboxylate;

161) [(1R)-1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]ethyl] (2S)-pyrrolidine-2-carboxylate;

162) tert-butyl 3-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-3-hydroxy-azetidine-1-carboxylate;

163) 1-ethyl-3-[5-[2-(3-hydroxyazetidin-3-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

164) 1-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

165) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-[[(2S)-pyrrolidine-2-carbonyl]amino]acetate;

166) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] (2S)-pyrrolidine-2-carboxylate;

167) 4-[3-[5-[7-[4-[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-pyridyl]-2-(ethylcarbamoylamino)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]oxetan-3-yl]oxy-4-oxo-butanoic acid;

168) 1-ethyl-3-[7-[5-(1-hydroxyethyl)-2-pyridyl]-5-[2-(1-hydroxyethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

169) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-(2-morpholinoethylamino)acetate;

170) 2-[[2-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethoxy]-2-oxo-ethyl]amino]acetic acid;

171) (2S)-2-amino-4-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethoxy]-4-oxo-butanoic acid;

172) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 4-aminobutanoate;

173) 1-ethyl-3-[5-[2-(4-hydroxy-1,1-dioxo-thian-4-yl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

174) 1-ethyl-3-[5-[2-(4-hydroxy-4-piperidyl)pyrimidin-5-yl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

175) 1-[7-[4-[(3-ethoxyazetidin-1-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

176) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-methoxy-1,3-benzothiazol-2-yl]urea;

177) 1-ethyl-3-[6-fluoro-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

178) 1-ethyl-3-[7-(3-fluoro-4-methoxy-2-pyridyl)-5-[2-[1-hydroxyethyl]pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

179) 3-[[2-[1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethoxy]-2-oxo-ethyl]amino]propanoic acid;

180) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] (3R)-pyrrolidine-3-carboxylate;

181) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] (3R)-morpholine-3-carboxylate;

182) 1-[6-(cyclopropylmethoxy)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

183) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-methoxyethoxy)-1,3-benzothiazol-2-yl]urea;

184) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] 2-(2-phosphonooxyethylamino)acetate;

185) 1-ethyl-3-[5-[2-[1-hydroxyethyl]pyrimidin-5-yl]-7-[4-(thiomorpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

186) 1-ethyl-3-[6-(2-hydroxyethoxy)-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

187) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-(thiomorpholinomethyl)-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

188) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(1-oxo-1,4-thiazinan-4-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

189) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-[2-methoxyethyl(methyl)amino]-1,3-benzothiazol-2-yl]urea;

190) [1-[5-[2-(ethylcarbamoylamino)-7-(2-pyridyl)-1,3-benzothiazol-5-yl]pyrimidin-2-yl]-1-methyl-ethyl] dihydrogen phosphate;

191) 1-[7-[4-[(1,1-dioxo-1,4-thiazinan-4-yl)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

192) 1-[6-[(3,4-dimethoxyphenyl)methoxy]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

193) 1-ethyl-3-[5-[2-[1-hydroxyethyl]pyrimidin-5-yl]-6-(tetrahydrofuran-2-ylmethoxy)-1,3-benzothiazol-2-yl]urea;

194) 1-ethyl-3-[5-[2-[1-hydroxyethyl]pyrimidin-5-yl]-6-morpholino-1,3-benzothiazol-2-yl]urea;

195) 1-[7-[(3S)-3-aminopyrrolidin-1-yl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]-3-ethyl-urea;

196) 1-ethyl-3-[7-[4-[(2-hydroxyethylamino)methyl]-2-pyridyl]-5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1,3-benzothiazol-2-yl]urea;

197) 1-ethyl-3-[5-[5-(1-hydroxyethyl)-3-pyridyl]-7-(2-pyridyl)-1,3-benzothiazol-2-yl]urea;

198) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[4-[(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)methyl]-2-pyridyl]-1,3-benzothiazol-2-yl]urea;

199) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-morpholinoethoxy)-1,3-benzothiazol-2-yl]urea;

200) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-methoxyethylsulfanyl)-1,3-benzothiazol-2-yl]urea;

201) 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-6-(2-methoxyethylsulfinyl)-1,3-benzothiazol-2-yl]urea; and

202) 1-ethyl-3-[5-[2-[(1R)-1-hydroxyethyl]pyrimidin-5-yl]-7-(5-methoxy-2-pyridyl)-1,3-benzothiazol-2-yl]urea;

salts, racemates, diastereomers, enantiomers, esters, carbamates, phosphates, sulfates, deuterated forms and prodrugs thereof.

18. A method for the treatment of a bacterial infection comprising administration of a compound as defined in any one of claims 1 to 17 or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulfate, deuterated form or prodrug thereof to a subject suffering from said infection.

19. A compound as defined in any one of claims 1 to 17 or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulfate, deuterated form or prodrug thereof for use in the treatment of a bacterial infection.

20. Use of a compound as defined in any one of claims 1 to 17 or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulfate, deuterated form or prodrug thereof in the preparation of a medicament for the treatment of a bacterial infection in a subject.

21. A method according to claim 18, a compound according to claim 19 or a use according to claim 20 wherein the bacterial infection is a Gram-positive infection, Gram-negative infection, community acquired bacterial pneumonia (CABP), hospital acquired bacterial pneumonia (HABP), or ventilator acquired bacterial pneumonia (VABP).

22. A method according to claim 18, a compound according to claim 19 or a use according to claim 20 wherein the bacterial infection is a respiratory infection, a skin or skin structure infection, a urinary tract infection, an intra-abdominal infection or a blood stream infection.

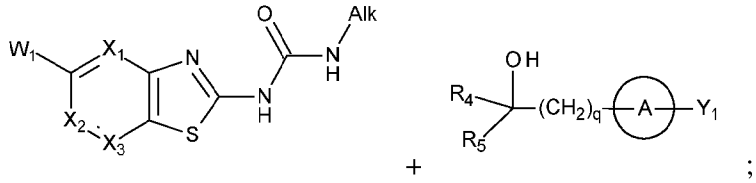
23. An antibacterial agent comprising a compound as defined in any one of claims 1 to 17 or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulfate, deuterated form or prodrug thereof.

24. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 17 or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulfate, deuterated form or prodrug thereof and an excipient or carrier.

25. A compound as defined in any one of claims 1 to 17 or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, ester, carbamate, phosphate, sulfate, deuterated form or prodrug thereof for use as a gyrase inhibitor.

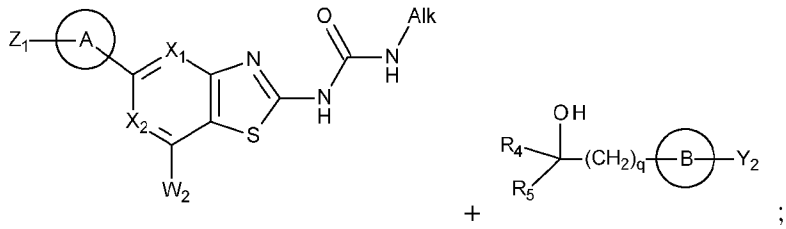
26. A process for the manufacture of a compound as defined in any one of claims 1 to 17 comprising the step(s) of:

coupling an intermediate of formula (i-a) with a precursor of formula (ii-a):



(i-a) (ii-a)

or alternatively coupling an intermediate of formula (i-b) with a precursor of formula (ii-b):



(i-b) (ii-b)

under coupling conditions wherein

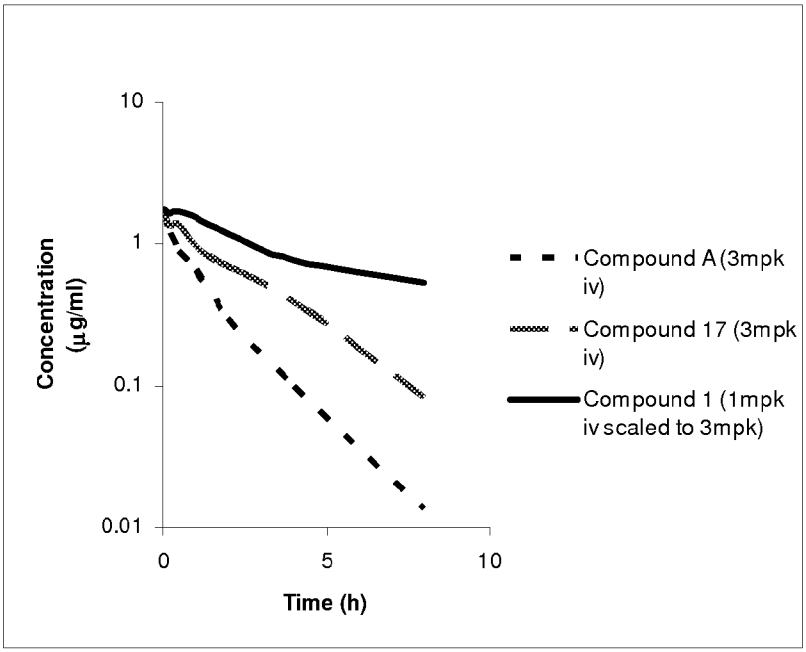
W_1 and W_2 are selected from halo, boronic acid or a boronate ester thereof, a stannylated moiety and triflate;

Y_1 and Y_2 are selected from H, halo, boronic acid or a boronate ester thereof, a stannylated moiety and triflate; and

ring A, ring B, Alk, X_1, X_2, X_3, R_4, R_5 and q are as defined in claim 1.

FIGURE 1

A


10
1
0.1
0.01
Concentration (µg/ml)
0
5
10
Time (h)
Compound A (3mpk iv)
Compound 17 (3mpk iv)
Compound 1 (1mpk iv scaled to 3mpk)

B

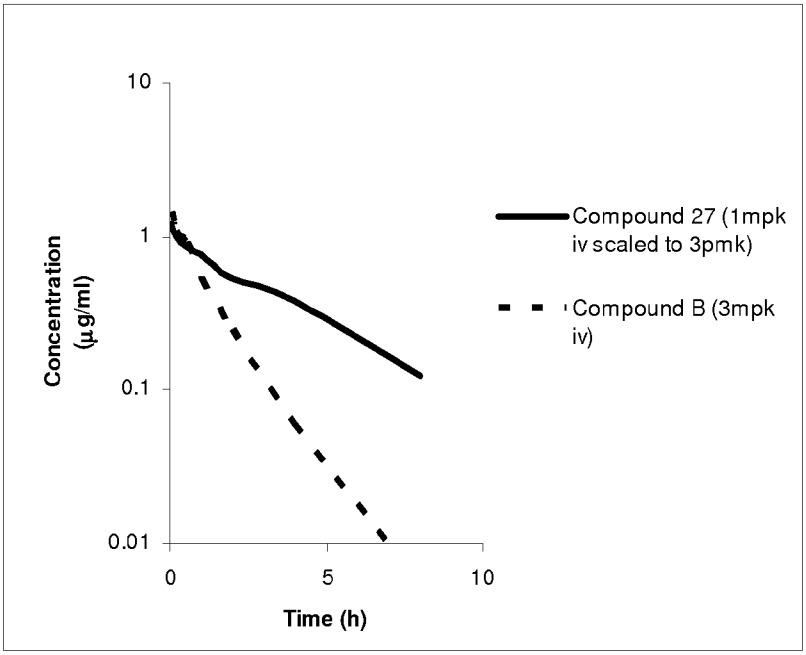
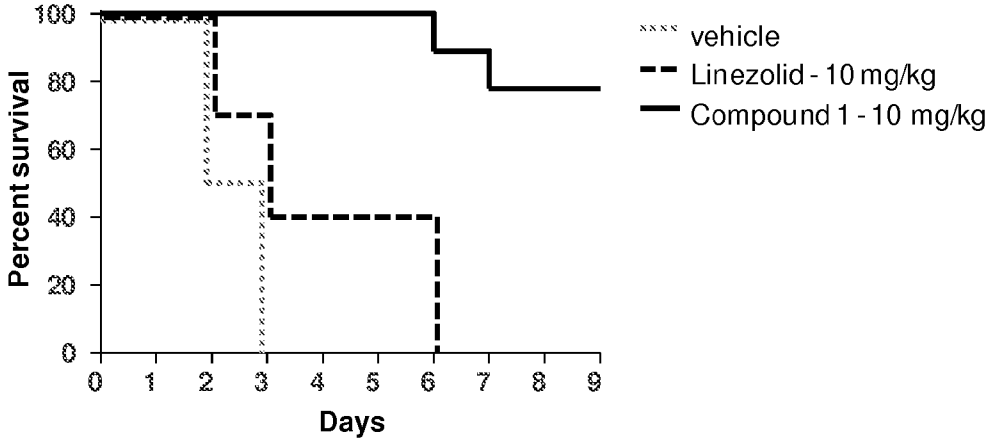

10
1
0.1
0.01
Concentration (µg/ml)
0
5
10
Time (h)
Compound 27 (1mpk iv scaled to 3pmk)
Compound B (3mpk iv)

FIGURE 2


100
80
60
40
20
0
Percent survival
0
1
2
3
4
5
6
7
8
9
Days
vehicle
Linezolid - 10 mg/kg
Compound 1 - 10 mg/kg

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2013/000286

A. CLASSIFICATION OF SUBJECT MATTER

C07D 417/14 (2006.01) C07D 417/02 (2006.01) A61K 31/429 (2006.01) A61P 31/04 (2006.01) A61K 31/428 (2006.01)

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)

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 practicable, search terms used)

CAPLUS and CAS Registry: Structure search based on compound of formula (I).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2013	25 July 2013
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au Facsimile No.: +61 2 6283 7999	Will Findlay AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262832018

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2013/000286**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/148093 A1 (PROLYSIS LTD.) 27 December 2007 See abstract, compound of formula (I) and compounds 18 and 19 (page 87), 34 (page 89), 57 and 58 (page 91), 144 (page 88)	1-26
X	WO 2009/156966 A1 (RANBAXY LABORATORIES LIMITED) 30 December 2009 & (CAS Registry number 1202806-47-0), (CAS Registry number 1202806-94-7), (CAS Registry number 1202807-06-4), (CAS Registry number 1202807-09-7) and (CAS Registry number 1202807-17-7) See abstract, compound of formula (I)	1-26
X	WO 2009/074812 A1 (PROLYSIS LTD.) 18 June 2009 & (CAS Registry number 1160790-32-8) and (CAS Registry number 1160790-47-5). See abstract, compound of formula (I)	1-26

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2013/000286**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2007/148093 A1	27 Dec 2007	AU 2007262791 B2	08 Nov 2012
		AU 2008334425 A1	18 Jun 2009
		BR PI0713501 A2	13 Mar 2012
		CA 2655403 A1	27 Dec 2007
		CN 101472585 A	01 Jul 2009
		EA 200900047 A1	30 Jun 2009
		EP 2034997 A1	18 Mar 2009
		EP 2034997 B1	17 Oct 2012
		JP 2009541289 A	26 Nov 2009
		KR 20090029817 A	23 Mar 2009
		MX 2008015706 A	31 Mar 2009
		NZ 574313 A	28 Oct 2011
		SG 172676 A1	28 Jul 2011
		US 2009197877 A1	06 Aug 2009
		US 7977340 B2	12 Jul 2011
		US 2011263590 A1	27 Oct 2011
		US 8389516 B2	05 Mar 2013
		US 2012004221 A1	05 Jan 2012
		US 8481544 B2	09 Jul 2013
		US 2010311766 A1	09 Dec 2010
		WO 2007148093 A1	27 Dec 2007
		WO 2009074810 A1	18 Jun 2009
		ZA 200900240 A	27 Jan 2010
WO 2009/156966 A1	30 Dec 2009	US 2011166088 A1	07 Jul 2011
		WO 2009156966 A1	30 Dec 2009
WO 2009/074812 A1	18 Jun 2009	CA 2709021 A1	18 Jun 2009
		CN 102015700 A	13 Apr 2011
		EA 201000993 A1	28 Feb 2011
		EA 018104 B1	30 May 2013
		EP 2231653 A1	29 Sep 2010
		EP 2231653 B1	03 Apr 2013
		JP 2011506417 A	03 Mar 2011
		KR 20100105847 A	30 Sep 2010
		MX 2010006428 A	30 Sep 2010
		NZ 586508 A	25 May 2012

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2013/000286**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		US 2010305067 A1	02 Dec 2010
		US 8299065 B2	30 Oct 2012
		WO 2009074812 A1	18 Jun 2009

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104302645 A
(43)申请公布日 2015.01.21

(21)申请号 201380014971.5

(22)申请日 2013.03.21

(30)优先权数据
61/614,044 2012.03.22 US

(85)PCT国际申请进入国家阶段日
2014.09.18

(86)PCT国际申请的申请数据
PCT/AU2013/000286 2013.03.21

(87)PCT国际申请的公布数据
WO2013/138860 EN 2013.09.26

(71)申请人 生物区欧洲有限公司
地址 英国牛津郡

(72)发明人 C·J·鲁尼斯 J·T·帕尔默
G·R·W·皮特 L·C·阿克斯福德
D·戴维斯

(74)专利代理机构 上海专利商标事务所有限公司 31100

代理人 余颖

(51)Int.Cl.
C07D 417/14(2006.01)
C07D 417/02(2006.01)
A61K 31/429(2006.01)
A61P 31/04(2006.01)
A61K 31/428(2006.01)

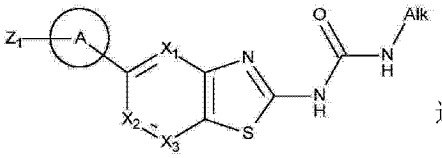
权利要求书17页 说明书123页 附图2页

(54)发明名称

抗菌化合物

(57)摘要

本发明提供了下式的化合物，其盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐/酯、磷酸盐/酯、硫酸盐/酯、氘代形式和前药。

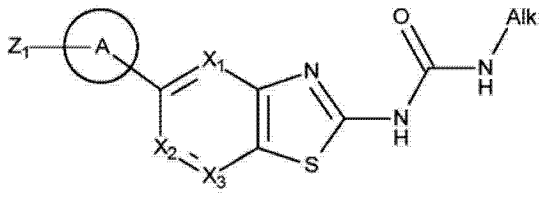


(I)

还提供了这些化合物作为抗菌剂的用途，包括其的组合物及其制造方法。

CN 104302645 A

1. 一种式 (I) 的化合物

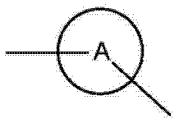


(I)

其盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药

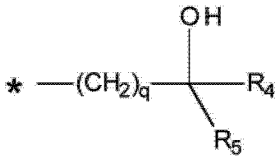
其中

X_1 是 N 或 C-R_1，其中 R_1 选自 H、OH、任选经取代的 C_{1-3} 烷基、任选经取代的 C_{2-3} 烯基、任选经取代的 C_{2-3} 炔基、任选经取代的 C_{1-3} 烷氧基、卤素、卤代 C_{1-3} 烷基、NH_2、任选经取代的 NHC_{1-3} 烷基、任选经取代的 $N(C_{1-3}$ 烷基 $)_2$、任选经取代的 SC_{1-3} 烷基和 CN；



表示环 A，其选自饱和或不饱和的 C_{3-7} 环烷基、饱和或不饱和的单环 3-7 元杂环、饱和或不饱和的稠合双环 C_{8-10} 环烷基、饱和或不饱和的稠合双环 8-10 元杂环、C_{6-10} 芳基和 5-10 元杂芳基并且可被任选取代；

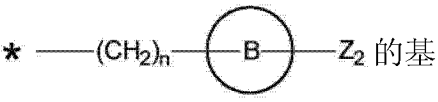
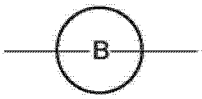
Z_1 是通式



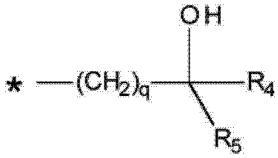
的仲或叔醇，如下文所定义的其酯、磷酸盐 / 酯、硫酸盐 / 酯或前药或者 Z_1 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基、CN 和任选经取代的 $(CH_2)_mNR^aR^b$，其中各 R^a 和 R^b 独立地选自 H、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{3-6} 环烷基和任选经取代的 4-6 元杂环或者 R^a 和 R^b 结合在一起以形成任选经取代的 4-6 元杂环，其中各 m 是独立地选自 0、1、2 和 3 的整数；

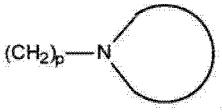
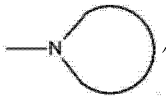
X_2 是 N 或 C-R_2，其中 R_2 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基、任选经取代的 $(CH_2)_mO(CH_2)_mC_{3-7}$ 环烷基、任选经取代的 $(CH_2)_mC_{3-7}$ 环烷基、任选经取代的 $(CH_2)_mO(CH_2)_m$ 苯基、任选经取代的 $(CH_2)_m$ 苯基、任选经取代的 $(CH_2)_mO(CH_2)_m$-5-10 元杂环、任选经取代的 $(CH_2)_m$-5-10 元杂环、卤素、任选经取代的卤代 C_{1-3} 烷基、CN 和任选经取代的 $(CH_2)_mNR^aR^b$；

X_3 是 N 或 C-R_3，其中 R_3 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基、任选经取代的 $(CH_2)_mO(CH_2)_mC_{3-7}$ 环烷基、任选经取代的 $(CH_2)_mC_{3-7}$ 环烷基、任选经取代的 $(CH_2)_mO(CH_2)_m$ 苯基、任选经取代的 $(CH_2)_m$ 苯基、任选经取代的

$(CH_2)_mO(CH_2)_m$-5-10 元杂环、任选经取代的 $(CH_2)_m$-5-10 元杂环、卤素、卤代 C_{1-3} 烷基、CN 和任选经取代的 $(CH_2)_mNR^aR^b$，或者 R_3 是式  的基团，其中 * 代表与 e 碳环原子相连的连接点；n 是选自 0、1、2 和 3 的整数；  代表环 B，其选自饱和或不饱和的单环 C_{3-7} 环烷基、饱和或不饱和的单环 3-7 元杂环、饱和或不饱和的稠合双环 C_{8-10} 环烷基、饱和或不饱和的稠合双环 8-10 元杂环、C_{6-10} 芳基和 5-10 元杂芳基并可被任选取代；以及

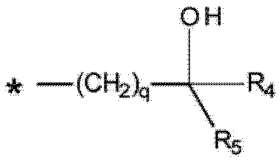
Z_2 是通式



的仲或叔醇、如下文所定义的其酯、磷酸盐 / 酯、硫酸盐 / 酯或前药或者 Z_2 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、$(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基、CN、任选经取代的 $(CH_2)_mNR^aR^b$，任选经取代的 $(CH_2)_p$-4-6 元杂环、任选经取代的 $(CH_2)_p$- 螺 - 双环 -7-11 元杂环和任选经取代的  其中 p 是选自 0、1、2 和 3 的整数且  代表任选经取代的 4-6 元杂环或任选经取代的螺双环 7-11 元杂环；以及

A1k 是任选经取代的 C_{1-6} 烷基、C_{2-6} 烯基、C_{2-6} 炔基、C_{3-6} 环烷基；以及

前提是 Z_1 或 Z_2 是通式



的仲或叔醇、其酯、磷酸盐 / 酯、硫酸盐 / 酯或前药，其中 q 是选自 0、1、2 和 3 的整数；

R_4 是 H 或选自任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_tOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tOC(=O)C_{1-6}$ 烷基、任选经取代的 $(CH_2)_tSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基和任选经取代的 $(CH_2)_tNR^aR^b$；

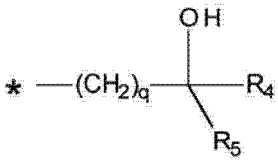
R_5 选自任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 C_{3-7} 环烷基环、任选经取代的苯基、任选经取代的 4-6 元杂环、任选经取代的 5-6 元杂芳环、任选经取代的 $(CH_2)_tOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tOC(=O)C_{1-6}$ 烷基、任选经取代的 $(CH_2)_tSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基和任选经取代的 $(CH_2)_mNR^aR^b$；

t 是选自 1、2、3、4、5 和 6 的整数；

或者 R_4 和 R_5 与其连接的碳原子形成任选经取代的 4-6 元杂环或 C_{3-7} 环烷基环；以及

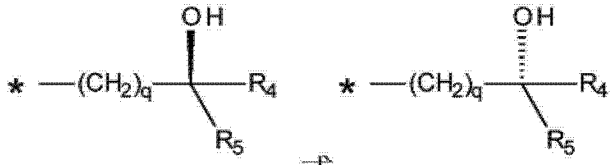
* 表示分别与环 A 或环 B 相连的连接点；此外各 (CH_2) 实体（如存在）可被独立地任选取代。

2. 如权利要求 1 所述的化合物，其中 Z_1 是通式



的仲醇或叔醇、其酯、氨基甲酸盐／酯、磷酸盐／酯、硫酸盐／酯或前药，其中 q、R_4、R_5 和 * 如权利要求 1 中所定义。

3. 如权利要求 1 或 2 所述的化合物，其中 Z_1 是通式



的手性醇或其酯、氨基甲酸盐／酯、磷酸盐／酯、硫酸盐／酯或前药，其中 q、R_4、R_5 和 * 如权利要求 1 所定义，前提是 R_4 和 R_5 是不同的。

4. 如权利要求 1-3 中任一项所述的化合物，其中 X_1 是 C-R_1、X_2 是 C-R_2 且 X_3 是 C-R_3。

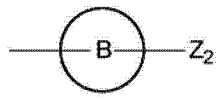
5. 如权利要求 1-4 中任一项所述的化合物，其中环 A 是任选经取代的 5-6 元杂芳基。

6. 如权利要求 1-5 中任一项所述的化合物，其中 X_1 是 C-R_1 且 R_1 是 H 或卤素。

7. 如权利要求 1-6 中任一项所述的化合物，其中 X_2 是 C-R_2 且 R_2 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 OC_{1-6} 烷基、任选经取代的 SC_{1-6} 烷基、任选经取代的 $S(=O)C_{1-6}$ 烷基、任选经取代的 5-6 元杂环、卤素、卤代 C_{1-3} 烷基、CN 和任选经取代的 $(CH_2)_mNR^aR^b$。

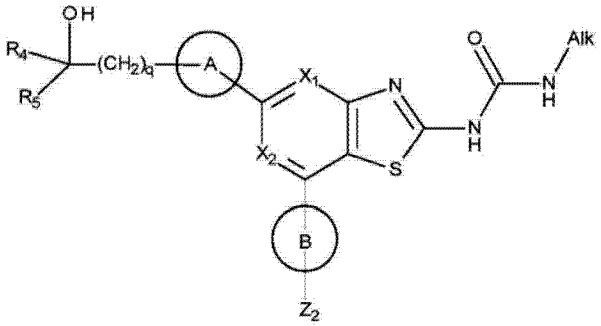
8. 如权利要求 1-7 中任一项所述的化合物，其中 X_3 是 C-R_3 且 R_3 是 H。

9. 如权利要求 1-7 中任一项所述的化合物，其中 X_3 是 C-R_3 且 R_3 选自任选经取代的 C_{1-3} 烷基、任选经取代的 OC_{1-3} 烷基、任选经取代的 $(CH_2)_mNH_2$、任选经取代的 $(CH_2)_mNHC_{1-3}$ 烷基和任选经取代的 $(CH_2)_mN(C_{1-3}$ 烷基$)_2$，其中 m 如权利要求 1 所定义。

10. 如权利要求 1-7 中任一项所述的化合物，其中 X_3 是 C-R_3 且 R_3 是如权利要求 1 所定义的式 

的基团。

11. 如权利要求 10 所述的化合物，所述化合物具有式 (II)：



(II)

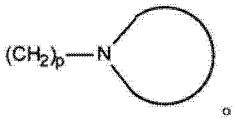
其盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药

其中 X_1、X_2、Alk、环 A、环 B、Z_2、R_4、R_5 和 q 如权利要求 1 所定义。

12. 如权利要求 1-11 中任一项所述的化合物，其中环 B 是任选经取代的 5-6 元杂芳基。

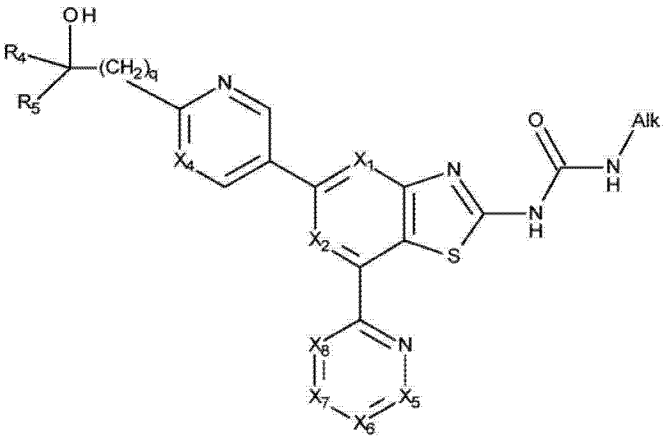
13. 如权利要求 1-12 中任一项所述的化合物，其中 Z_2 是 H。

14. 如权利要求 1-12 中任一项所述的化合物，其中 Z_2 选自 OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基、$(CH_2)_mNH_2$、任选经取代的 $(CH_2)_mNHC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mN(C_{1-6}$ 烷基 $)_2$、任选经取代的 $(CH_2)_p$-4-6 元杂环、任选经取代的 $(CH_2)_p$- 螺 - 双环 -7-11 元杂环和任选经取代的



。

15. 如权利要求 1 所述的化合物，所述化合物具有式 (III)：



(III)

其盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药

其中 X_1、X_2、Alk、R_4、R_5 和 q 如权利要求 1 所定义；

X_4 是 N、CH、C- 卤素或 C-C_{1-3} 烷氧基；

X_5、X_6、X_7 和 X_8 各自独立地选自 N、C-H 或 C-Z_2，其中 Z_2 如权利要求 1 所定义，前提是 X_5、

X_6、X_7 或 X_8 中不超过一个是 N。

16. 如权利要求 1-15 中任一项所述的化合物，其中 q 是 0。

17. 如权利要求 1 所述的化合物，所述化合物选自：

1) 1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲；

2) 1- 乙基 -3-[7-[4-[(3- 羟基 -3- 甲基 - 氮杂环丁烷 -1- 基）甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲；

3) 1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-6-(四氢呋喃 -2- 基甲氧基)-1,3- 苯并噻唑 -2 基] 脲；

4) 1- 乙基 -3-[6- 氟 -5-[6-[羟基 (3- 吡啶基）甲基]-3- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲；

5) 1-(2- 羟基乙基)-3-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲；

6) 1- 乙基 -3-[5-[5-(1- 羟基乙基）吡嗪 -2- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲；

7) 1-[5-[2-[(1S*,2R*)-1,2- 二羟基丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲（混合物 1-[5-[2-[(1S,2R)-1,2- 二羟基丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲；和 1-[5-[2-[(1R,2S)-1,2- 二羟基丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲）；

8) 1-[5-[2-[(3R*,4S*)-3,4- 二羟基四氢吡喃 -4- 基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲（混合物 1-[5-[2-[(3R,4S)-3,4- 二羟基四氢吡喃 -4- 基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲；以及 1-[5-[2-[(3S,4R)-3,4- 二羟基四氢吡喃 -4- 基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲）；

9) 1- 乙基 -3-[5-[4-(1- 羟基乙基）三唑 -1- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲；

10) 1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-7- 嘧啶 -2- 基 -1,3- 苯并噻唑 -2 基] 脲；

11) 1- 乙基 -3-[5-[4-(1- 羟基 -1- 甲基 - 乙基）咪唑 -1- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲；

12) 1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-7- 甲氧基 -1,3- 苯并噻唑 -2- 基] 脲；

13) 1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-7-(甲氧基甲基)-1,3- 苯并噻唑 -2- 基] 脲；

14) 1- 乙基 -3-[5-[2-(1- 羟基乙基）嘧啶 -5- 基]-7-[(6- 甲基 -3- 吡啶基）甲氧基]-1,3- 苯并噻唑 -2- 基] 脲；

15) 1- 乙基 -3-[5-[2-(1- 羟基乙基）嘧啶 -5- 基]-7-[4-(甲基硫烷基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲；

16)1- 乙基 -3-[5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-7-[4-(甲基亚磺酰基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

17)1- 乙基 -3-[5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

18)1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基 4- 甲基哌嗪 -1- 羧酸酯 ;

19)4-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙氧基]-4- 氧代 - 丁酸 ;

20)04-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙基]01- 甲基丁二酸酯 ;

21)4-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙氧基]-4- 氧代 - 丁酸 ;

22)1- 乙基 -3-[5-[2-[(1R)-1- 羟基乙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

23)1- 乙基 -3-[5-[2-[(1S)-1- 羟基乙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

24)1- 乙基 -3-[5-[6-[羟基 -(1- 甲基咪唑 -2- 基) 甲基]-3- 吡啶基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

25)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[5-(吗啉基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

26)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-(吡咯烷 -1- 基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

27)1- 乙基 -3-[5-[6-(1- 羟基 -1- 甲基 - 乙基)-3- 吡啶基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

28)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-(吗啉基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

29)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-[(3- 羟基吡咯烷 -1- 基) 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

30)1- 乙基 -3-[7-[4-[(3- 羟基氮杂环丁烷 -1- 基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲 ;

31)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-[(3- 甲氧基氮杂环丁烷 -1- 基) 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

32)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-(2- 吗啉基乙氧基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

33)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-(1- 吗啉基乙基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

34)1-[7-[4-[(3,3- 二氟吡咯烷 -1- 基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

35)1- 乙基 -3-[7-[4-[[(3S)-3- 氟吡咯烷 -1- 基] 甲基]-2- 吡啶基]-5-[2-(1- 羟

基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲 ;

36)1- 乙基 -3-[7-[4-[[(3R)-3- 氟吡咯烷 -1- 基] 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲 ;

37)1-[7-[4-[(3,3- 二氟 -1- 哌啶基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

38)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-(3- 吗啉基丙氧基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

39)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7- 吡嗪 -2- 基 -1,3- 苯并噻唑 -2 基] 脲 ;

40)1-[5-[2-(1,2- 二羟基乙基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

41)1-[7-(二甲基氨基甲基)-6- 羟基 -5-[6-(1- 羟基 -1- 甲基 - 乙基)-3- 吡啶基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

42)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-[[(3R)-3- 甲氧基吡咯烷 -1- 基] 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

43)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-(6- 甲基嘧啶 -4- 基)-1,3- 苯并噻唑 -2- 基] 脲 ;

44)1- 乙基 -3-[6- 羟基 -5-[6-(1- 羟基 -1- 甲基 - 乙基)-3- 吡啶基]-7-(吗啉基甲基)-1,3- 苯并噻唑 -2- 基] 脲 ;

45)1-[6-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-3- 吡啶基]-4- 甲基 - 哌啶 -4- 羧酸 ;

46)2-[6-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-3- 吡啶基] 乙酸 ;

47)1- 乙基 -3-[5-[2-(1- 羟基环己基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

48)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 噻唑 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

49)1- 乙基 -3-[5-[5-(1- 羟基 -1- 甲基 - 乙基) 吡嗪 -2- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

50)1-[2-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-4- 吡啶基]-4- 甲基 - 哌啶 -4- 羧酸 ;

51)1-[6-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-2- 吡啶基]-4- 甲基 - 哌啶 -4- 羧酸 ;

52)1-[4-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基] 嘧啶 -2- 基]-4- 甲基 - 哌啶 -4- 羧酸 ;

53)1-[7-[4-[(环丙基氨基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

54)4-[[2-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-4- 吡啶基] 氨基]-1- 甲基 - 环己烷羧酸 ;

55)1- 乙基 -3-[5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-7-[4-(吗啉基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

56)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[5-(2- 吗啉基乙氧基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

57)1-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 丙基 - 脲 ;

58)1-[5-[2-[环丙基 (羟基) 甲基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

59)1- 乙基 -3-[5-[2-(1- 羟基丙基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

60)1- 乙基 -3-[5-[2-(1- 羟基 -2,2- 二甲基 - 丙基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

61)1- 乙基 -3-[5-[2-(1- 羟基丁基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

62)[(1R)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基](2R)-2- 氨基 -3- 甲基 - 丁酸酯 ;

63)[(1S)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基](2R)-2- 氨基 -3- 甲基 - 丁酸酯 ;

64)1- 乙基 -3-[7-[4-[[(3S)-3- 氟吡咯烷 -1- 基] 甲基]-2- 吡啶基]-5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲 ;

65)1- 乙基 -3-[7-[4-[(3- 羟基氮杂环丁烷 -1- 基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲 ;

66)1- 乙基 -3-[5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-7-[4-[(3- 羟基 -3- 甲基 - 氮杂环丁烷 -1- 基) 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

67)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-[(3- 羟基 -3- 甲基 - 吡咯烷 -1- 基) 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

68)1- 乙基 -3-[5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-7-[4-[(3- 甲基吗啉 -4- 基) 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

69)1-[7-[4-[[(2R,6S)-2,6- 二甲基吗啉 -4- 基] 甲基]-2- 吡啶基]-5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

70)1- 乙基 -3-[5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-7-[4-[(2,2,3,3,5,5,6,6- 八氘代吗啉 -4- 基) 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

71)1-[7-[4-[(2,5- 二甲基吗啉 -4- 基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

72)(2S)-1-[[2-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-4- 吡啶基] 甲基] 吡咯烷 -2- 羧酸 ;

73)1- 乙基 -3-[5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-7-[4-(6- 氧杂 -2- 氮杂螺 [3.3] 庚烷 -2- 基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

74)1-[5-[2-(乙基氨甲酰基氨基)-7-[4-(1- 羟基 -1- 甲基 - 乙基)-2- 吡啶

基]-1,3-苯并噻唑-5-基]嘧啶-2-基]-4-甲基-哌啶-4-羧酸；

75)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(2-吗啉基乙氧基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

76)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-[(3-甲氧基氮杂环丁烷-1-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

77)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-[[(3R)-3-羟基吡咯烷-1-基]甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

78)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(2-甲氧基乙基氨基)嘧啶-2-基]-1,3-苯并噻唑-2-基]脲；

79)1-乙基-3-[7-[4-(4-乙基哌嗪-1-基)嘧啶-2-基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

80)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(2-甲氧基乙氧基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

81)1-乙基-3-[5-[2-(1-羟基-2-吗啉基-乙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

82)1-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-甲基-脲；

83)1-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-甲基-脲；

84)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-[(3-羟基-3-甲基-吡咯烷-1-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

85)1-乙基-3-[7-[4-(2-羟基乙基氨基)嘧啶-2-基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

86)1-乙基-3-[7-[4-(3-羟基-3-甲基-氮杂环丁烷-1-基)嘧啶-2-基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

87)1-[6-[2-(乙基氨甲酰基氨基)-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-7-基]嘧啶-4-基]-4-甲基-哌啶-4-羧酸；

88)1-[5-[2-(乙基氨甲酰基氨基)-7-[4-(1-羟基乙基)-2-吡啶基]-1,3-苯并噻唑-5-基]嘧啶-2-基]-4-甲基-哌啶-4-羧酸；

89)[1-[5-[2-(乙基氨基甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]4-甲基哌嗪-1-羧酸酯；

90)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-(4-羟基-2-吡啶基)-1,3-苯并噻唑-2-基]脲；

91)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(2-吗啉基乙基氨基)嘧啶-2-基]-1,3-苯并噻唑-2-基]脲；

92)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(2-甲氧基乙氧基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

93)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-[(3-甲氧基氮杂环丁烷-1-基)嘧啶-2-基]-1,3-苯并噻唑-2-基]脲；

94)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-(4-吗啉基嘧啶-2-基)-1,3-苯并噻唑-2-基]脲；

95)1-乙基-3-[5-[6-(1-羟基乙基)-3-吡啶基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

96)1-乙基-3-[7-(2-吡啶基)-5-[6-(2,2,2-三氟-1-羟基-乙基)-3-吡啶基]-1,3-苯并噻唑-2-基]脲；

97)1-[2-[2-(乙基氨甲酰基氨基)-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-7-基]嘧啶-4-基]-4-甲基-哌啶-4-羧酸；

98)1-乙基-3-[5-[2-(1-乙基-1-羟基-丙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

99)1-[5-[2-(乙基氨甲酰基氨基)-7-[5-(1-羟基-1-甲基-乙基)-2-吡啶基]-1,3-苯并噻唑-5-基]嘧啶-2-基]-4-甲基-哌啶-4-羧酸；

100)1-[7-[4-(二乙氧基磷酰基甲基)-2-吡啶基]-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

101)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(吗啉基甲基)嘧啶-2-基]-1,3-苯并噻唑-2-基]脲；

102)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[6-(吗啉基甲基)吡嗪-2-基]-1,3-苯并噻唑-2-基]脲；

103)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[(2-羟基-2-甲基-丙基)氨基]嘧啶-2-基]-1,3-苯并噻唑-2-基]脲；

104)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(四氢呋喃-2-基甲氧基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

105)1-乙基-3-[7-[4-(3-羟基氮杂环丁烷-1-基)嘧啶-2-基]-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

106)1-乙基-3-[7-(5-氟-4-吗啉基-嘧啶-2-基)-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

107)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[4-(2-甲氧基乙基)哌嗪-1-基]嘧啶-2-基]-1,3-苯并噻唑-2-基]脲；

108)1-乙基-3-[7-[4-(吗啉基甲基)-2-吡啶基]-5-[6-(2,2,2-三氟-1-羟基-乙基)-3-吡啶基]-1,3-苯并噻唑-2-基]脲；

109)1-[6-[2-(乙基氨甲酰基氨基)-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-7-基]嘧啶-4-基]-4-甲基-哌啶-4-羧酸；

110)1-[2-[2-(乙基氨甲酰基氨基)-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-7-基]-4-吡啶基]哌啶-4-羧酸；

111)1-乙基-3-[5-[2-(4-羟基四氢吡喃-4-基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

112)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(2-氧杂-7-氮杂螺[3.5]壬烷-7-基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

113)1-乙基-3-[5-[2-(3-羟基氧杂环丁烷-3-基)嘧啶-5-基]-7-(2-吡啶

基)-1,3- 苯并噻唑 -2- 基] 脲 ;

114)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-[(3- 甲氧基 -3- 甲基 - 氮杂环丁烷 -1- 基) 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

115)1- 乙基 -3-[5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-7- 嘧啶 -2- 基 -1,3- 苯并噻唑 -2- 基] 脲 ;

116)1- 乙基 -3-[7-[4-(2- 吗啉基乙氧基)-2- 吡啶基]-5-[6-(2,2,2- 三氟 -1- 羟基 - 乙基)-3- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

117)1-[2-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基] 嘧啶 -4- 基]-4- 甲基 - 哌啶 -4- 羧酸 ;

118)1-[5-[2-[(1R*,2R*)-1,2- 二羟基丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 (混合物 1-[5-[2-[(1R,2R)-1,2- 二羟基丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ; 和 1-[5-[2-[(1S,2S)-1,2- 二羟基丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲) ;

119)1- 乙基 -3-[5-[2-(1- 羟基环戊基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

120)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[5-(吗啉基甲基) 嘧啶 -2- 基]-1,3- 苯并噻唑 -2- 基] 脲 ;

121)1- 乙基 -3-[5-[2-[(1R)-1- 羟基乙基] 嘧啶 -5- 基]-7-[4-(吗啉基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

122)1- 乙基 -3-[5-[2-[(1S)-1- 羟基乙基] 嘧啶 -5- 基]-7-[4-(吗啉基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

123)4-[3-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 氧杂环丁烷 -3- 基] 氧基 -4- 氧代 - 丁酸 ;

124)4-[2-[5-[2-(乙基氨基甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-2- 羟基 - 丙氧基]-4- 氧代 - 丁酸 ;

125)1- 乙基 -3-[5-[2-(4- 羟基四氢吡喃 -4- 基) 嘧啶 -5- 基]-7-[4-(吗啉基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

126)1-[5-[2-(乙基氨基甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基 2- 氨基乙酸酯 ;

127)1- 乙基 -3-[5-[2-(4- 羟基四氢噻喃 -4- 基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

128)1- 乙基 -3-[5-[2-(4- 羟基 -1- 甲基 -4- 哌啶基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

129)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙基]2-(2- 氨基乙基氨基) 乙酸酯 ;

130)1-[5-[2-[(1R*,2S*)-3,3- 二氟 -1,2- 二羟基 - 丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 (混合物 1-[5-[2-[(1R,2S)-3,3- 二氟 -1,2- 二羟基 - 丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ; 和

1-[5-[2-[(1S,2R)-3,3-二氟-1,2-二羟基-丙基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲)；

131)1-乙基-3-[7-(2-吡啶基)-5-[2-[(1R*,2S*)-3,3,3-三氟-1,2-二羟基-丙基]嘧啶-5-基]-1,3-苯并噻唑-2-基]脲(混合物1-乙基-3-[7-(2-吡啶基)-5-[2-[(1R,2S)-3,3,3-三氟-1,2-二羟基-丙基]嘧啶-5-基]-1,3-苯并噻唑-2-基]脲;和1-乙基-3-[7-(2-吡啶基)-5-[2-[(1S,2R)-3,3,3-三氟-1,2-二羟基-丙基]嘧啶-5-基]-1,3-苯并噻唑-2-基]脲)；

132)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基](2S)-2-氨基丙酸酯；

133)4-[(1S)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙氧基]-4-氧代-丁酸；

134)4-[(1R)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙氧基]-4-氧代-丁酸；

135)1-[5-[2-(1,2-二羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(吗啉基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

136)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基2-氨基-2-甲基-丙酸酯；

137)1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基3-氨基丙酸酯；

138)叔丁基4-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-4-羟基-哌啶-1-羧酸酯；

139)1-乙基-3-[5-[2-(4-羟基-1-氧代-硫杂环戊烷-4-基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

140)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]2-(二甲基氨基)乙酸酯；

141)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]2-吗啉基乙酸酯；

142)1-[7-[4-[[(2R,6S)-2,6-二甲基吗啉-4-基]甲基]-2-吡啶基]-5-[2-[(1R)-1-羟基乙基]嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

143)1-[7-[4-[[(2R,6S)-2,6-二甲基吗啉-4-基]甲基]-2-吡啶基]-5-[2-[(1S)-1-羟基乙基]嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

144)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]5-氨基戊酸酯；

145)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]5-(二甲基氨基)戊酸酯；

146)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]2-氨基乙酸酯；

147)1-[7-[4-[(3,3-二氟氮杂环丁烷-1-基)甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

148)1-[7-[4-[[(2R,6S)-2,6-二甲基吗啉-4-基]甲基]-2-吡啶基]-5-[2-(3-羟基氧杂环丁烷-3-基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

149)1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基磷酸二氢酯；

150)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-6-(2-甲氧基乙基氨基)-1,3-苯并噻唑-2-基]脲；

151)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-吗啉基-1,3-苯并噻唑-2-基]脲；

152)[(1R)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基]磷酸二氢酯；

153)[(1S)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基]磷酸二氢酯；

154)1-乙基-3-[5-[2-(3-羟基氧杂环丁烷-3-基)嘧啶-5-基]-7-[4-(吗啉基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

155)1-乙基-3-[7-[4-[(3-甲氧基氮杂环丁烷-1-基)甲基]-2-吡啶基]-5-[6-(2,2,2-三氟-1-羟基-乙基)-3-吡啶基]-1,3-苯并噻唑-2-基]脲；

156)1-[7-[4-[(4,4-二氟-1-哌啶基)甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

157)1-[5-[2-(1,2-二羟基-1-甲基-乙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲；

158)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-(5-甲基-2-吡啶基)-1,3-苯并噻唑-2-基]脲；

159)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[(4-甲基哌嗪-1-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

160)[(1S)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基](2S)-吡咯烷-2-羧酸酯；

161)[(1R)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基](2S)-吡咯烷-2-羧酸酯；

162)叔丁基3-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-3-羟基-氮杂环丁烷-1-羧酸酯；

163)1-乙基-3-[5-[2-(3-羟基氮杂环丁烷-3-基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

164)1-[7-[4-[[(2R,6S)-2,6-二甲基吗啉-4-基]甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

165)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]2-[[(2S)-吡咯烷-2-羰基]氨基]乙酸酯；

166)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基](2S)-吡咯烷-2-羧酸酯；

167)4-[3-[5-[7-[4-[[(2R,6S)-2,6-二甲基吗啉-4-基]甲基]-2-吡啶基]-2-(乙

基氨甲酰基氨基)-1,3-苯并噻唑-5-基]嘧啶-2-基]氧杂环丁烷-3-基]氧基-4-氧代-丁酸;

168)1-乙基-3-[7-[5-(羟基乙基)-2-吡啶基]-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲;

169)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]2-(2-吗啉基乙基氨基)乙酸酯;

170)2-[[2-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙氧基]-2-氧代-乙基]氨基]乙酸;

171)(2S)-2-氨基-4-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙氧基]-4-氧代-丁酸;

172)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]4-氨基丁酸酯;

173)1-乙基-3-[5-[2-(4-羟基-1,1-二氧代-硫杂环戊烷-4-基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲;

174)1-乙基-3-[5-[2-(4-羟基-4-哌啶基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲;

175)1-[7-[4-[(3-乙氧基氮杂环丁烷-1-基)甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲;

176)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-6-甲氧基-1,3-苯并噻唑-2-基]脲;

177)1-乙基-3-[6-氟-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲;

178)1-乙基-3-[7-(3-氟-4-甲氧基-2-吡啶基)-5-[2-[1-羟基乙基]嘧啶-5-基]-1,3-苯并噻唑-2-基]脲;

179)3-[[2-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙氧基]-2-氧代-乙基]氨基]丙酸;

180)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基](3R)-吡咯烷-3-羧酸酯;

181)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基](3R)-吗啉基-3-羧酸酯;

182)1-[6-(环丙基甲氧基)-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲;

183)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-6-(2-甲氧基乙氧基)-1,3-苯并噻唑-2-基]脲;

184)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]2-(2-膦酰氧基乙基氨基)乙酸酯;

185)1-乙基-3-[5-[2-[1-羟基乙基]嘧啶-5-基]-7-[4-(硫代吗啉基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲;

186)1-乙基-3-[6-(2-羟基乙氧基)-5-[2-(1-羟基-1-甲基-乙基)嘧

啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲；

187)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-(硫代吗啉基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲；

188)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-[(1- 氧代 -1,4- 噻嗪 -4- 基) 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲；

189)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-6-[2- 甲氧基乙基 (甲基) 氨基]-1,3- 苯并噻唑 -2- 基] 脲；

190)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙基] 磷酸二氢酯；

191)1-[7-[4-[(1,1- 二氧代 -1,4- 噻嗪 -4- 基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲；

192)1-[6-[(3,4- 二甲氧基苯基) 甲氧基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲；

193)1- 乙基 -3-[5-[2-[1- 羟基乙基] 嘧啶 -5- 基]-6-(四氢呋喃 -2- 基甲氧基)-1,3- 苯并噻唑 -2- 基] 脲；

194)1- 乙基 -3-[5-[2-[1- 羟基乙基] 嘧啶 -5- 基]-6- 吗啉基 -1,3- 苯并噻唑 -2- 基] 脲；

195)1-[7-[(3S)-3- 氨基吡咯烷 -1- 基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲；

196)1- 乙基 -3-[7-[4-[(2- 羟基乙基氨基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲；

197)1- 乙基 -3-[5-[5-(1- 羟基乙基)-3- 吡啶基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲；

198)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-[(2,2,3,3,5,5,6,6- 八氘代吗啉 -4- 基) 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲；

199)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-6-(2- 吗啉基乙氧基)-1,3- 苯并噻唑 -2- 基] 脲；

200)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-6-(2- 甲氧基乙基硫烷基)-1,3- 苯并噻唑 -2- 基] 脲；

201)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-6-(2- 甲氧基乙基亚磺酰基)-1,3- 苯并噻唑 -2- 基] 脲；

202)1- 乙基 -3-[5-[2-[(1R)-1- 羟基乙基] 嘧啶 -5- 基]-7-(5- 甲氧基 -2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲；

其盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药。

18. 一种处理细菌性感染的方法，所述方法包括对患有所述感染的对象给予权利要求 1-17 中任一项所定义的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式或前药。

19. 用于处理细菌性感染的权利要求 1-17 中任一项所定义的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式或前药。

20. 权利要求 1-17 中任一项所定义的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式或前药在用于制备处理对象所患细菌性感染的药物中的用途。

21. 如权利要求 18 所述的方法、权利要求 19 所述的化合物或权利要求 20 所述的用途，所述细菌性感染是革兰氏阳性感染、革兰氏阴性感染、社区获得性细菌性肺炎 (CABP)、医院获得性细菌性肺炎 (HABP) 或呼吸机获得性细菌性肺炎 (VABP)。

22. 如权利要求 18 所述的方法、权利要求 19 所述的化合物或权利要求 20 所述的用途，所述细菌性感染是呼吸道感染、皮肤或皮肤结构感染、尿道感染、腹内感染或血流感染。

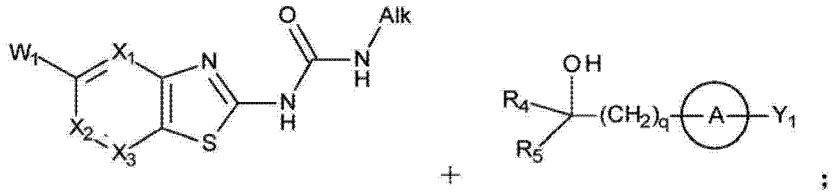
23. 一种抗菌试剂，所述试剂包括权利要求 1-17 中任一项所定义的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式或前药。

24. 一种药物组合物，所述试剂包括权利要求 1-17 中任一项所定义的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式或前药以及赋形剂或载剂。

25. 用作促旋酶抑制剂的权利要求 1-17 中任一项所定义的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式或前药。

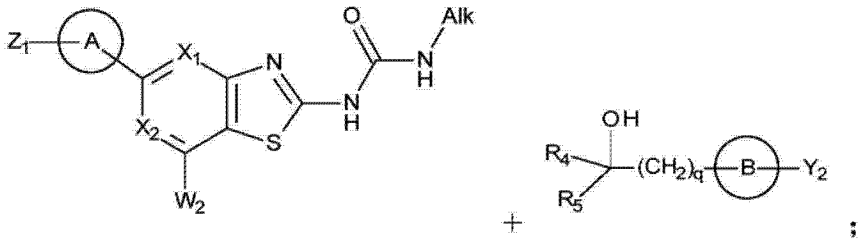
26. 一种制造权利要求 1-17 中任一项所定义的化合物的方法，所述方法包括以下步骤：

在偶联条件下将式 (i-a) 的中间体与式 (ii-a) 的前体偶联：



(i-a)　　(ii-a)

或者将式 (i-b) 的中间体与式 (ii-b) 的前体偶联：



(i-b)　　(ii-b)

其中

W_1 和 W_2 选自卤素、硼酸或其硼酸酯、甲锡烷基化部分和三氟甲磺酸酯；

Y_1 和 Y_2 选自 H、卤素、硼酸或其硼酸酯、甲锡烷基化部分和三氟甲磺酸酯；以及

环 A、环 B、Alk、X_1、X_2、X_3、R_4、R_5 和 q 如权利要求 1 所定义。

抗菌化合物

技术领域

[0001] 本发明涉及新种类的化合物、其作为抗菌剂的用途，包括其的组合物及其制造方法。

[0002] 背景

[0003] II 型拓扑异构酶通过使得一个 DNA 片段运送通过另一个的方式催化 DNA 拓扑异构体的互换。细菌编码两种 II 型拓扑异构酶，DNA 促旋酶和 DNA 拓扑异构酶 IV。促旋酶控制 DNA 的超螺旋并且缓解拓扑压力。复制后，拓扑异构酶 IV 使子染色体脱连环，并且还能使超螺旋 DNA 松弛。

[0004] 细菌 II 型拓扑异构酶形成由两个亚基组成的异源四聚体复合物。促旋酶形成了由 GyrA 和 GyrB 组成的 A_2B_2 复合物，而拓扑异构酶形成了由 ParC 和 ParE 组成的 C_2E_2 复合物。相反地，真核 II 型拓扑异构酶是同源二聚体。理想地，基于抑制细菌 II 型拓扑异构酶的抗生素对于细菌酶会有选择性，而针对真核 II 型拓扑异构酶相对无活性。

[0005] 所述 II 型拓扑异构酶是高度保守的酶，能据此设计广谱抑制剂。另外，所述 GyrB 和 ParE 亚基功能上相似，在 N 末端结构域和 C 末端结构域具有与其他亚基（分别是 GyrA 和 ParC）和 DNA 相互作用的 ATP 酶结构域。促旋酶和拓扑异构酶 IV 活性位点之间的守恒暗示了这些位点的抑制剂可同时靶向两种 II 型拓扑异构酶。这类双重靶向抑制剂具有吸引力，因为其具有降低建立基于靶标抗性的潜力。

[0006] II 型拓扑异构酶是多种抗细菌剂的靶标。这些试剂中最重要的是喹诺酮。原始的喹诺酮抗生素包含萘啶酸、西诺沙星和恶喹酸。氟的加入产生了新药物种类－氟喹诺酮，其有更广的抗菌谱和改善的药代动力学特性。所述氟喹诺酮包含诺氟沙星、环丙沙星、和第四代喹喏酮加替沙星和莫西沙星。香豆素和环噻啶类（cyclothialidine）是抑制 II 型拓扑异构酶的其他抗生素种类，然而由于其在细菌中的渗透性差、具有真核毒性且水溶性低，它们并没有得到广泛使用。这种抗生素的示例包含新生霉素和香豆霉素 A1、环噻啶（cyclothialidine）、西诺啶（cinodine）和克来罗西汀。

[0007] 目前，利奈唑胺是对于革兰氏阳性细菌所致急性细菌性皮肤和皮肤结构感染（ABSSSI）的标准治疗。其属于噁唑烷酮类化合物，并且是一种蛋白合成抑制剂。

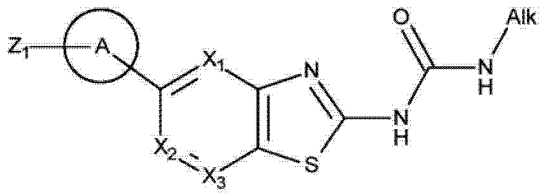
[0008] 然而，抗生素抗性的连续出现要求持续开发新种类的抗生素，并且需要抑制细菌拓扑异构酶的替代化合物。

[0009] WO2007/148093、WO2009/074812、WO2009/074810 和 WO2012/045124 描述了申请人的较早期化合物，其能够抑制细菌促旋酶活性。如今，申请人已发现一类包含碳环或杂环的相关化合物（所述碳环或杂环包括支链，即仲或叔醇取代基）及其前药，其可能赋予化合物优点。一种或多种优点包括所需的药代动力学特性、前药性、溶解性和引入手性以提供另一亚类活性对映异构体。

发明内容

[0010] 根据第一方面，提供了式（I）的化合物

[0011]

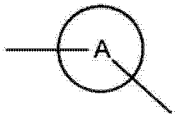


(I)

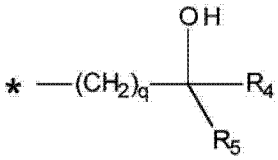
[0012] 其盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药。

[0013] 其中

[0014] X_1 是 N 或 C-R_1，优选 C-R_1，其中 R_1 选自 H、OH、任选经取代的 C_{1-3} 烷基、任选经取代的 C_{2-3} 烯基、任选经取代的 C_{2-3} 炔基、任选经取代的 C_{1-3} 烷氧基、卤素、卤代 C_{1-3} 烷基、NH_2、任选经取代的 NHC_{1-3} 烷基、任选经取代的 $N(C_{1-3}$ 烷基 $)_2$、任选经取代的 SC_{1-3} 烷基和 CN；

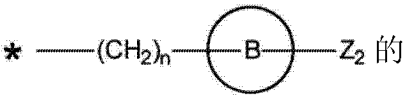
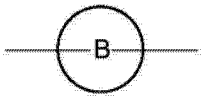
[0015]  表示环 A，其选自饱和或不饱和的单环 C_{3-7} 环烷基、饱和或不饱和的单环 3-7 元杂环、饱和或不饱和的稠合双环 C_{8-10} 环烷基、饱和或不饱和的稠合双环 8-10 元杂环、C_{6-10} 芳基和 5-10 元杂芳基并可被任选取代；

[0016] Z_1 是通式

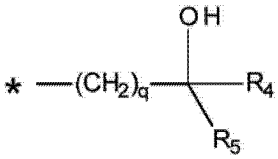
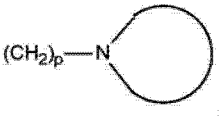
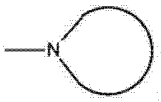
[0017]  的仲或叔醇、如下文所定义的其酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯或前药，或者 Z_1 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基卤素、任选经取代的卤代 C_{1-3} 烷基、CN 和任选经取代的 $(CH_2)_mNR^aR^b$，其中各 R^a 和 R^b 独立地选自 H、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{3-6} 环烷基和任选经取代的 4-6 元杂环，或者 R^a 和 R^b 结合在一起以形成任选经取代的 4-6 元杂环，其中各 m 是独立地选自 e、1、2 和 3 的整数；

[0018] X_2 是 N 或 C-R_2，优选 C-R_2，其中 R_2 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基、任选经取代的 $(CH_2)_mO(CH_2)_mC_{3-7}$ 环烷基、任选经取代的 $(CH_2)_mC_{3-7}$ 环烷基、任选经取代的 $(CH_2)_mO(CH_2)_m$ 苯基、任选经取代的 $(CH_2)_m$ 苯基、任选经取代的 $(CH_2)_mO(CH_2)_m$-5-10 元杂环、任选经取代的 $(CH_2)_m$-5-10 元杂环、卤素、任选经取代的卤代 C_{1-3} 烷基、CN 和任选经取代的 $(CH_2)_mNR^aR^b$；

[0019] X_3 是 N 或 C-R_3，优选 C-R_3，其中 R_3 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基、任选经取代的 $(CH_2)_mO(CH_2)_mC_{3-7}$ 环烷基、任选经取代的 $(CH_2)_mC_{3-7}$ 环烷基、任选经取代的 $(CH_2)_mO(CH_2)_m$ 苯基、任选经取代的 $(CH_2)_m$ 苯基、任选经取代的 $(CH_2)_mO(CH_2)_m$-5-10 元杂环、任选经取代的 $(CH_2)_m$-5-10 元杂环、卤素、任选经取代

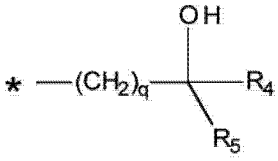
的卤代 C_{1-3} 烷基、CN 和任选经取代的 $(CH_2)_mNR^aR^b$，或者 R_3 是式  的基团，其中 * 表示与 C 环原子相连的连接点；n 是选自 0、1、2 和 3 的整数；  表示环 B，其选自饱和或不饱和的单环 C_{3-7} 环烷基、饱和或不饱和的单环 3-7 元杂环、饱和或不饱和的稠合双环 C_{8-10} 环烷基、饱和或不饱和的稠合双环 8-10 元杂环、C_{6-10} 芳基和 5-10 元杂芳基并可被任选取代；以及

[0020] Z_2 是通式

[0021]  的仲或叔醇或如下文所定义的其酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯或前药，或者 Z_2 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基、CN、任选经取代的 $(CH_2)_mNR^aR^b$，任选经取代的 $(CH_2)_p$-4-6 元杂环、任选经取代的 $(CH_2)_p$- 螺 - 双环 -7-11 元杂环和任选经取代的  其中 p 是选自 0、1、2 和 3 的整数且  表示任选经取代的 4-6 元杂环或任选经取代的螺双环 7-11 元杂环；以及

[0022] Alk 是任选经取代的 C_{1-6} 烷基、C_{2-6} 烯基、C_{2-6} 炔基、C_{3-6} 环烷基；以及

[0023] 前提是 Z_1 或 Z_2 是通式

[0024]  的仲或叔醇、如下文所定义的其酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯或前药，其中 q 是选自 0、1、2 和 3 的整数，优选 q 是 0；

[0025] R_4 是 H 或选自任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_tOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tOC(=O)C_{1-6}$ 烷基、任选经取代的 $(CH_2)_tSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基和任选经取代的 $(CH_2)_tNR^aR^b$；

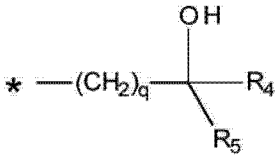
[0026] R_5 选自任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 C_{3-7} 环烷基环、任选经取代的苯基、任选经取代的 4-6 元杂环、任选经取代的 5-6 元杂芳环、任选经取代的 $(CH_2)_tOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tOC(=O)C_{1-6}$ 烷基、任选经取代的 $(CH_2)_tSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基和任选经取代的 $(CH_2)_tNR^aR^b$；

[0027] t 是选自 1、2、3、4、5 和 6 的整数；

[0028] 或者 R_4 和 R_5 与其连接的碳原子形成任选经取代的 4-6 元杂环或 C_{3-7} 环烷基环；以及

[0029] ＊表示分别与环 A 或环 B 相连的连接点；此外其中各 (CH_2) 实体（若存在）可被独立地任选取代。在一个实施方式中，提供了式 (I) 的化合物、其盐和前药。

[0030] 在一个实施方式中，Z_1 是通式

[0031] 

的仲或叔醇或其前药，所述前药选自由羟基部分所形成的酯、氨基甲酸盐 / 酯、磷酸盐 / 酯或硫酸盐 / 酯。

[0032] 根据第二方面，提供了治疗细菌性感染的方法，所述方法包括对患有所述感染的对象给予式 (I) 的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药。在一个实施方式中，所述感染是革兰氏阳性菌感染。在另一个实施方式中，革兰氏阳性感染是由选自金黄色葡萄球菌 (S.aureus)、粪肠球菌 (E.faecalis) 和化脓链球菌 (S.pyogenes)（甚至更优选金黄色葡萄球菌）的细菌菌株引起的。在另一个实施方式中，所述感染是革兰氏阴性菌感染。在另一个实施方式中，革兰氏阴性感染是由流感嗜血杆菌 (H.influenzae)、鲍式不动杆菌 (A.baumannii)、大肠杆菌 (E.coli)、肺炎克雷伯菌 (K.pneumoniae)、嗜肺军团菌 (Legionella pneumophila)、粘膜炎莫拉菌 (Moraxella catarrhalis) 和淋病奈瑟球菌 (Neisseria gonorrhoeae) 的细菌菌株引起的。

[0033] 根据第三方面，提供了式 (I) 的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药，用于细菌性感染的治疗。

[0034] 根据第四方面，提供了抗菌剂，所述抗菌剂包括式 (I) 的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药。

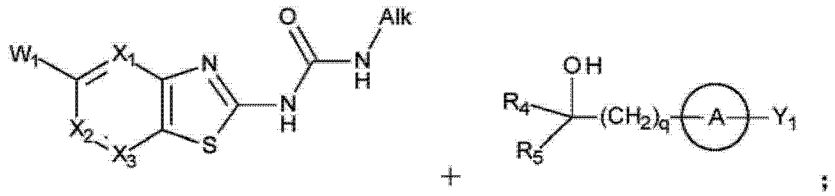
[0035] 根据第五方面，提供了组合物，所述组合物包括式 (I) 的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药以及赋形剂或载剂。在一个实施方式中，所述组合物是药物组合物，所述盐是药学上可接受的盐并且所述赋形剂或载剂是药学上可接受的。

[0036] 根据第六方面，提供了式 (I) 的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药，用作促旋酶抑制剂。在一个实施方式中，式 (I) 的化合物具有抗 ATP 酶的活性。

[0037] 根据第七方面，提供了一种生产方法，用于生产式 (I) 的化合物、其盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药，所述方法包括以下步骤：

[0038] 在偶联条件下将式 (i-a) 的中间体与式 (ii-a) 的前体偶联：

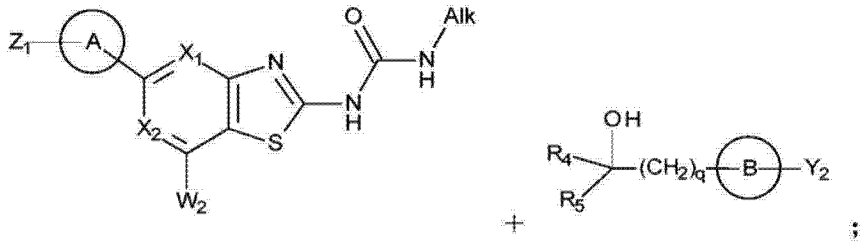
[0039]



(i-a) (ii-a)

[0040] 或者将式 (i-b) 的中间体与式 (ii-b) 的前体偶联：

[0041]



(i-b) (ii-b)

[0042] 其中

[0043] W_1 和 W_2 选自卤素（优选 Cl、Br 和 I）、硼酸或其硼酸酯、甲锡烷基化部分和三氟甲磺酸酯；

[0044] Y_1 和 Y_2 选自 H、卤素（优选 Cl、Br 和 I）、硼酸或其硼酸酯、甲锡烷基化部分和三氟甲磺酸酯；以及

[0045] 环 A、环 B、Alk、X_1、X_2、X_3、R_4、R_5 和 q 如前文所定义。

[0046] 在一个实施方式中，所述方法包括形成羟基（醇）部分的酯、氨基甲酸盐／酯、磷酸盐／酯或硫酸盐／酯的额外步骤。

[0047] 根据第八方面，提供了处理基质中细菌污染的方法，所述方法包括向这种污染位点施加足够量的式 (I) 的化合物，其外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐／酯、磷酸盐／酯、硫酸盐／酯或氘代形式以抑制细菌生长。

[0048] 根据第九方面，提供了式 (I) 的化合物或其药学上可接受的盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐／酯、磷酸盐／酯、硫酸盐／酯、氘代形式和前药在药物制备中的用法，所述药物用于对象中细菌性感染的治疗。

附图说明

[0049] 图 1：显示了大鼠试验中的静脉内 (IV) 药代动力学概况，其中 X 轴表示时间（小时）且 Y 轴表示血浆浓度（μg/mL），其中 (A) 比较化合物 A 与本发明的化合物 1 和 17，(B) 比较化合物 B 与本发明的化合物 27。

[0050] 图 2：显示了肺炎链球菌 (S. pneumoniae) 9 天肺感染模型中以 10mg/kg 的剂量静脉给予化合物 1 或利奈唑胺后的小鼠存活率，其中 X 轴表示天数且 Y 轴表示存活百分比。

[0051] 发明详述

[0052] 本发明是基于被发现具有定靶促旋酶活性的新的一类化合物。因此，在一个实施方式中，式 (I) 的化合物用于调节促旋酶活性，更具体地作为促旋酶抑制剂。该类化合物

还表现出抗菌活性，更具体地是针对革兰氏阳性和 / 或革兰氏阴性种类的菌株，如葡萄球菌、肠球菌、链球菌和嗜血菌，例如金黄色葡萄球菌 (Staphylococcus aureus)、表皮葡萄球菌 (Staphylococcus epidermidis)、酿脓链球菌 (Streptococcus pyogenes)、肺炎链球菌 (Streptococcus pneumoniae)、流感嗜血菌 (Haemophilus influenzae)、大肠杆菌 (Escherichia coli)、肺炎杆菌 (pneumoniae)、嗜肺军团菌 (Legionella pneumophila)、粘膜炎莫拉菌 (Moraxella catarrhalis) 和淋病奈瑟球菌 (Neisseria gonorrhoeae)。因此，本发明涉及的化合物用于细菌性感染或污染的处理，例如在革兰氏阳性感染、革兰氏阴性感染和社区获得性细菌性肺炎 (CABP)、医院获得性细菌性肺炎 (HABP) 和呼吸机获得性细菌性肺炎 (VABP) 的治疗中。因此，在一个实施方式中，式 (I) 化合物用于治疗由革兰氏阳性菌株引起的细菌感染。在另一个实施方式中，式 (I) 化合物用于治疗由革兰氏阴性菌株引起的细菌感染。细菌感染的位点有许多且包括呼吸道感染、尤其是肺感染、皮肤和皮肤结构感染、尿道感染、腹内感染和血流（败血症）感染。抗菌耐药性的发展在医院环境中特别常见。因此，医院患者尤其处于被耐药细菌菌株感染的风险中。

[0053] 定义

[0054] 除非在本文中另有定义，应理解以下术语具有以下通用含义。

[0055] 术语“C_{1-6} 烷基”包括任选经取代的直链或支链烃基，其具有 1、2、3、4、5 或 6 个碳原子或包含这些整数中的任意两个的范围。示例包括甲基 (Me)、乙基 (Et)、丙基 (Pr)、异丙基 (i-Pr)、丁基 (Bu)、异丁基 (i-Bu)、仲丁基 (s-Bu)、叔丁基 (t-Bu)、戊基、新戊基、己基等。除非本文另外说明，术语“C_{1-6} 烷基”也包括含有缺少一个氢原子的烷基基团，该基团通过两个位置连接，即二价。这类基团也称为“C_{1-6} 亚烷基”基团。优选 C_{1-3} 烷基和 C_{1-3} 亚烷基基团。

[0056] 术语“C_{2-6} 烯基”表示任选经取代的直链或支链烃基，在适当处其具有至少一个 E 或 Z 立体化学结构的双键或并且具有 2、3、4、5 或 6 个碳原子或包含这些整数中任意两个的范围。示例包括乙烯基、1- 丙烯基、1- 和 2- 丁烯基、2- 甲基 -2- 丙烯基、己烯基、丁二烯基、己二烯基、己三烯基等。除非本文另外说明，术语“C_{1-6} 烯基”还包括含有缺少一个氢原子的烯基基团，该基团通过两个位置连接，即二价。这类基团也称为“C_{2-6} 亚烯基”基团。优选 C_{2-3} 烯基和 C_{2-3} 亚烯基基团。

[0057] 术语“C_{2-6} 炔基”表示任选经取代的直链或支链烃基，其具有至少一个三键并且具有 2、3、4、5 或 6 个碳原子或包含这些整数中任意两个的范围。示例包括乙炔基、1- 丙炔基、1- 和 2- 丁炔基、2- 甲基 -2- 丙炔基、2- 戊炔基、3- 戊炔基、4- 戊炔基、2- 己炔基、3- 己炔基、4- 己炔基、5- 己炔基等。除非本文另外说明，术语“C_{2-6} 炔基”也包括含有缺少一个氢原子的炔基基团，该基团通过两个位置连接，即二价。这类基团也称为“C_{2-6} 亚炔基”基团。优选 C_{2-3} 炔基和 C_{2-3} 亚炔基基团。

[0058] 术语“C_{3-8} 环烷基”表示非芳族环状烃基，其具有 3、4、5、6、7 或 8 个碳原子或包含这些整数中任意两个的范围，包括环丙基、环丁基、环戊基、环己基、环己烯基、环庚基等。应理解环烷基可以是饱和的（如环己基）或不饱和的（如环己烯基）。优选 C_{3-6} 环烷基基团。

[0059] 术语“羟基”表示 -OH 基团。

[0060] 术语“氧代”表示＝ O 基团。

[0061] 术语“C_{1-6} 烷氧基”是指 OC_{1-6} 烷基基团。示例包括甲氧基、乙氧基、丙氧基、异丙氧

基、丁氧基、叔-丁氧基、戊氧基等。氧原子可以位于烃链上，并且不需要是将基团与该化合物的其他部分连接的原子。优选 C_{1-3} 烷氧基基团。

[0062] 术语“芳氧基”是指 -O 芳基基团并且可以包括其变体，诸如“烷氧基芳基”，其中芳基如本文定义。示例包括但不限于苯氧基和萘氧基和苄氧基。

[0063] 术语“卤代”、“卤素”、“卤化”和相似的术语是指氟、氯、溴和碘 (F,Cl,Br,I)。

[0064] 术语“C_{1-6} 烷基卤代”是指被一个或多个卤素取代的 C_{1-6} 烷基。优选 C_{1-3} 烷基卤代基团，例如 $-CHF_2$ 和 $-CF_3$。

[0065] 术语“C_{1-6} 烷氧基卤代”是指被一个或多个卤素取代的 C_{1-6} 烷氧基。优选 C_{1-3} 烷氧基卤代基团，例如 $-OCHF_2$ 和 $-OCF_3$。

[0066] 术语“羧酸盐/酯”或“羧基”是指 $-COO^-$ 或 -COOH 基团。

[0067] 术语“酯”是指这样的羧基基团，它的氢被如下基团取代：例如 C_{1-6} 烷基基团（“羧基 C_{1-6} 烷基”或“烷基酯”）、芳基或芳烷基基团（“芳基酯”或“芳烷基酯”）。示例包括但不限于 CO_2C_{1-3} 烷基基团，例如甲酯 (CO_2Me)、乙酯 (CO_2Et) 和丙酯 (CO_2Pr) 并且包括其逆酯 (reverse ester)（例如，-OCOMe、-OCOEt 和 -OCOPr）。

[0068] 术语“氰基”是指 -CN 基团。

[0069] 术语“硝基”是指 $-NO_2$ 基团。

[0070] 术语“氨基”指 $-NH_2$ 基团。

[0071] 术语“取代的氨基”或“仲氨基”是指这样的氨基基团，它的氢被如下基团取代：例如 C_{1-6} 烷基基团（“C_{1-6} 烷基氨基”）、芳基或芳烷基基团（“芳基氨基”、“芳烷基氨基”）。优选 C_{1-3} 烷基氨基基团，例如甲基氨基 (NHMe)、乙基氨基 (NHEt) 和丙基氨基 (NHPr)。

[0072] 术语“双取代的氨基”或“叔氨基”是指这样的氨基基团，它的两个氢被如下基团取代：例如相同或不同的 C_{1-6} 烷基基团（“二烷基氨基”）、芳基和烷基基团（“芳基（烷基）氨基”）等。优选二 (C_{1-3} 烷基）氨基基团，例如二甲基氨基 (NMe_2)、二乙基氨基 (NEt_2)、二丙基氨基 (NPr_2) 及其变体（例如 N(Me)(Et) 等）。

[0073] 术语“酰基”或“醛”是指 -C(=O)H 基团。

[0074] 术语“取代的酰基”或“酮”是指这样的酰基基团，它的氢被如下基团取代：例如 C_{1-6} 烷基基团（“C_{1-6} 烷基酰基”或“烷基酮”或“酮烷基”）、芳基基团（“芳基酮”）、芳烷基基团（“芳烷基酮”）等。优选 C_{1-3} 烷基酰基基团。

[0075] 术语“酰氨基”或“酰胺”是指 $-C(O)NH_2$ 基团。

[0076] 术语“氨酰基”是指 -NHC(O)H 基团。

[0077] 术语“取代的酰氨基”或“取代的酰胺”是指这样的酰氨基基团，它的氢被如下基团取代：例如 C_{1-6} 烷基基团（“C_{1-6} 烷基酰氨基”或“C_{1-6} 烷基酰胺”）、芳基（“芳基酰氨基”）、芳烷基基团（“芳烷基酰氨基”）等。优选 C_{1-3} 烷基酰胺基基团，例如甲酰胺 (-C(O)NHMe)、乙酰胺 (-C(O)NHEt) 和丙酰胺 (-C(O)NHPr) 并且包括其逆酰胺 (reverse amide)（例如，-NHMeC(O)-、-NHEtC(O)- 和 -NHPrC(O)-）。

[0078] 术语“双取代的酰氨基”或“双取代的酰胺”是指这样的酰氨基基团，它的两个氢被如下基团取代：例如 C_{1-6} 烷基基团（“二 (C_{1-6} 烷基）酰氨基”或“二 (C_{1-6} 烷基）酰胺”）、芳烷基和烷基基团（“烷基（芳烷基）酰氨基”）等。优选二 (C_{1-3} 烷基）酰胺基团，例如二甲酰胺 ($-C(O)NMe_2$)、二乙酰胺 ($-C(O)NEt_2$) 和二丙酰胺 ($-C(O)NPr_2$) 及其变体（例如，-C(O)

N(Me)Et 等）并且包括其逆酰胺。

[0079] 术语“氨基甲酸”指 NH_2CO_2H 基团。

[0080] 术语“氨基甲酸盐／酯”是指这样的氨基甲酸基团，它的一个或全部两个氨基氢被如下基团独立取代：例如 C_{1-6} 烷基基团（“C_{1-6} 烷基氨基甲酸盐／酯”）、芳基（“芳基氨基甲酸盐／酯”）、芳烷基基团（“芳烷基氨基甲酸盐／酯”）等。

[0081] 术语“硫醇”是指 -SH 基团。

[0082] 术语“C_{1-6} 烷基硫代”是指氢被 C_{1-6} 烷基基团取代的硫醇基团。优选 C_{1-3} 烷基硫代基团，例如硫甲基、硫乙基和硫丙基。

[0083] 术语“硫代”是指＝S 基团。

[0084] 术语“亚磺酰基”是指 -S(＝O)H 基团。

[0085] 术语“取代的亚磺酰基”或“亚砜”是指这样的亚磺酰基基团，它的氢被如下基团取代：例如 C_{1-6} 烷基基团（“C_{1-6} 烷基亚磺酰基”或“C_{1-6} 烷基亚砜”）、芳基（“芳基亚磺酰基”）、芳烷基（“芳烷基亚磺酰基”）等。优选 C_{1-3} 烷基亚磺酰基基团，例如 -SO 甲基、-SO 乙基和 -SO 丙基。

[0086] 术语“磺酰基”是指 $-SO_2H$ 基团。

[0087] 术语“取代的磺酰基”是指这样的磺酰基基团，它的氢被如下基团取代：例如 C_{1-6} 烷基基团（“磺酰基 C_{1-6} 烷基”）、芳基（“芳基磺酰基”）、芳烷基（“芳烷基磺酰基”）等。优选磺酰基 C_{1-3} 烷基基团，例如 $-SO_2Me$、$-SO_2Et$ 和 $-SO_2Pr$。

[0088] 术语“磺酰氨基”或“磺酰胺”是指 $-SO_2NH_2$ 基团。

[0089] 术语“取代的磺酰氨基”或“取代的磺酰胺”是指这样的磺酰氨基基团，它的氢被如下基团取代：例如 C_{1-6} 烷基基团（“磺酰氨基 C_{1-6} 烷基”）、芳基（“芳基磺酰胺”）、芳烷基（“芳烷基磺酰胺”）等。优选磺酰氨基 C_{1-3} 烷基基团，例如 $-SO_2NHMe$、$-SO_2NHEt$ 和 $-SO_2NHPr$ 并且包括其逆磺酰胺 (reverse sulfonamide)（例如，$-NHSO_2Me$、$-NHSO_2Et$ 和 $-NHSO_2Pr$）。

[0090] 术语“双取代的磺酰氨基”或“双取代的磺酰胺”是指这样的磺酰氨基基团，他的两个氢被如下基团取代：例如可以是相同或不同的 C_{1-6} 烷基基团（“磺酰氨基二 (C_{1-6} 烷基)”）、芳烷基和烷基基团（“磺酰氨基（芳烷基）烷基”）等。优选磺酰氨基二 (C_{1-3} 烷基）基团，例如 $-SO_2NMe_2$、$-SO_2NEt_2$ 和 $-SO_2NPr_2$ 及其变体（例如，$-SO_2N(Me)Et$ 等）并且包括其逆磺酰胺 (reserve sulfonamide)。

[0091] 术语“硫酸盐／酯”是指 $OS(O)_2OH$ 基团并且包括氢被如下基团取代的那些：例如 C_{1-6} 烷基基团（“烷基硫酸盐／酯”）、芳基（“芳基硫酸盐／酯”）、芳烷基（“芳烷基硫酸盐／酯”）等。优选 C_{1-3} 硫酸盐／酯，例如 $OS(O)_2OMe$、$OS(O)_2OEt$ 和 $OS(O)_2OPr$。

[0092] 术语“磺酸盐／酯”是指 SO_3H 基团并且包括氢被如下基团取代的那些：例如 C_{1-6} 烷基基团（“烷基磺酸盐／酯”）、芳基（“芳基磺酸盐／酯”）、芳烷基（“芳烷基磺酸盐／酯”）等。优选 C_{1-3} 磺酸酯，诸如，例如 SO_3Me、SO_3Et 和 SO_3Pr。

[0093] 术语“磷酸盐／酯”是指 $-OP(O)(OH)_2$ 基团并且包括各个氢被如下基团独立地取代的那些：例如 C_{1-6} 烷基基团（“烷基磷酸盐／酯”）、芳基（“芳基磷酸盐／酯”）、芳烷基（“芳烷基磷酸盐／酯”）等。

[0094] 术语“膦酸盐／酯”是指 $-P(O)(OH)_2$ 基团并且包括氢被如下基团独立地取代的那些：例如 C_{1-6} 烷基基团（“烷基膦酸盐／酯”）、芳基（“芳基膦酸盐／酯”）、芳烷基（“芳烷

基膦酸盐 / 酯”）等。

[0095] 术语“芳基”是指任意含有碳环（非 - 杂环）芳族环的基团并且可以是单环、双环或三环体系。芳族环或环体系通常由 6 或 10 个碳原子组成。这样的基团可以含有稠环体系（诸如萘基、四氢萘基、芴基、茚基、蒽基、蒽基等），连环系统（诸如联苯基基团），并且可以是取代或未取代的。芳基的示例包括但不限于苯基、联苯基、萘基和四氢萘基。优选苯基。

[0096] 术语“芳烷基”是指被 C_{1-6} 烷基基团取代的芳基。示例包括苄基和苯乙基。

[0097] 术语“杂环基”是指通过从杂环化合物的环原子上去除氢原子得到的部分，该杂环部分具有 3 至 10 个环原子（除非另外说明），其中 1、2、3 或 4 个是环杂原子，各杂原子独立选自 O、S 和 N。

[0098] 在本文中，前缀 3、4、5、6、7、8、9 和 10 元表示环原子的数量或环原子的范围，包括碳原子或杂原子。例如，本文所用术语“3-10 元杂环”涉及具有 3、4、5、6、7、8、9 或 10 个环原子或包括这些整数中任意两个的范围的杂环基团。杂环基团的示例包括 5-6 元单环杂环基和 9-10 元稠合双环杂环基。

[0099] 单环杂环基团的示例包括，但不限于含有一个氮原子的那些，诸如氮丙啶（3 元环）、氮杂环丁烷（4 元环）、吡咯烷（四氢吡咯）、吡咯啉（例如，3- 吡咯啉、2,5- 二氢吡咯）、2H- 吡咯或 3H- 吡咯（异吡咯）或吡咯烷酮（5 元环）、哌啶、二氢吡啶、四氢吡啶（6 元环）、吖庚因（7 元环）；含有两个氮原子的那些，诸如咪唑啉、吡唑烷（二氮杂环戊烷 (diazolidine)）、咪唑啉、吡唑啉（二氢吡唑）(5 元环）、哌嗪（6 元环）；含有一个氧原子的那些，诸如环氧乙烷（3 元环）、氧杂环丁烷（4 元环）、环氧丁烷（四氢呋喃）、呋喃（二氢呋喃）(5 元环）、噁烷（四氢吡喃）、二氢吡喃、吡喃（6 元环）、氧杂䓬（7 元环）；含有两个氧原子的那些，诸如二氧戊环（5 元环）、二噁烷（6 元环）和二氧杂环庚烷（7 元环）；含有三个氧原子的那些，诸如三噁烷（6 元环）；含有一个硫原子的那些，诸如硫杂丙环（3 元环）、硫杂环丁烷（4 元环）、四氢硫杂茂 (thiolane)（四氢噻吩）(5 元环）、硫杂环戊烷 (thiane)（四氢噻喃）(6 元环）、硫杂环庚烷 (thiepane) (7 元环）；含有一个氮原子和一个氧原子的那些，诸如四氢噁唑、二氢噁唑、四氢异噁唑、二氢异噁唑（5 元环）、吗啉、四氢噁嗪、二氢噁嗪、噁嗪（6 元环）；含有一个氮原子和一个硫原子的那些，诸如噻唑啉、噻唑烷（5 元环）、硫代吗啉（6 元环）；含有两个氮原子和一个氧原子的那些，诸如噁二嗪（6 元环）；含有一个氧原子和一个硫原子的那些，诸如：氧硫杂环戊二烯 (oxathiole) (5 元环）和氧硫杂环己烷（噻噁烷）(6 元环）；以及含有一个氮原子、一个氧原子和一个硫原子的那些，诸如氧杂噻嗪（6 元环）。

[0100] 杂环基也包括芳族杂环基和非芳族杂环基。这类基团可以是取代的或未取代的。

[0101] 术语“芳族杂环基”可以与术语“杂芳族”或术语“杂芳基”或“杂芳”互换使用。在芳族杂环基团中的杂原子可以独立地选自 N、S 和 O。

[0102] 本文使用的“杂芳基”表示具有芳族特征的杂环基团并且包括含有一个或多个芳族环的芳族单环体系和多环（如双环）体系。术语芳族杂环基也包括假芳族杂环基。术语“假芳族”是指并非严格芳族的环体系，但是通过电子的非定域作用的方式稳定并且以与芳族环相似的方式作用。因此术语芳族杂环基包括多环体系，其中所有的稠环是芳族的并且在一个或多个环是非芳族的环系统中至少一个环是芳族的环体系。在同时含有稠合在一起的芳族环和非芳族环的多环体系中，基团可以通过芳族环或非芳族环与另一个部分连接。

[0103] 杂芳基基团的示例是含有五至十个环原子的单环和双环基团。杂芳基基团可以是，例如，由稠合的 5 元和 6 元环或两个稠合的 6 元环或两个稠合的 5 元环形成的 5 元或 6 元的单环或双环结构。各环可以含有最多四个通常选自氮、硫和氧的杂原子。杂芳环会含有最多 4 个杂原子，更通常最多 3 个杂原子，更通常最多 2 个，例如单个杂原子。在一个实施方式中，杂芳环含有至少一个环氮原子。在杂芳环中的氮原子可以是碱性的，如在咪唑或吡啶的情况中，或基本非碱性的，如在吲哚或吡咯氮的情况中。通常在杂芳基中存在的碱性氮原子，包括环的任意氨基基团取代基的数量会少于 5 个。

[0104] 芳族杂环基可以是 5 元或 6 元单环芳族环系统。

[0105] 5 元单环杂芳基的示例包括，但不限于呋喃基、噻吩基、吡咯基、噁唑基、噁二唑基（包括 1,2,3 和 1,2,4 噁二唑基以及呋咱基，例如 1,2,5- 噁二唑基）、噻唑基、异噁唑基、异噻唑基、吡唑基、咪唑基、三唑基（包括 1,2,3、1,2,4 和 1,3,4 三唑基）、噁三唑基、四唑基、噻二唑基（包括 1,2,3 和 1,3,4 噻二唑基）等。

[0106] 6 元单环杂芳基的示例包括，但不限于吡啶基、嘧啶基、哒嗪基、吡嗪基、三嗪基、吡喃基、噁嗪基、二噁英基 (dioxinyl)、噻嗪基、噻二嗪基等。含氮的 6 元杂芳基的示例包括吡啶基 (1 个氮）、吡嗪基、嘧啶基和哒嗪基 (2 个氮）。应理解例如在吡啶基的情况中，当由氧代（＝O) 取代时，该基团可互换地指代吡啶酮基团。

[0107] 芳族杂环基团也可以是双环或多环杂芳族环体系，如稠环体系（包括嘌呤、蝶啶基、二氮杂萘基、1H 噻吩并 [2,3-c] 吡唑基、噻吩并 [2,3-b] 呋喃基等）或连环体系（如低聚噻吩、聚吡咯等）。稠环体系也可以包括与如苯基、萘基、茚基、薁基、芴基、蒽基等的碳环芳族环稠合的 5 元或 6 元杂环，如与苯环稠合的 5 元或 6 元芳族杂环，包括与苯环稠合的含氮 5 元芳族杂环，与苯环稠合的含 1 或 2 个氮的 5 元芳族杂环和如与 6 元芳族或非芳族杂环稠合的 5 元或 6 元芳族杂芳基。

[0108] 双环杂芳基基团可以例如选自下基团 ;a) 与含有 1、2 或 3 个环杂原子的 5 元或 6 元环稠合的苯环 ;b) 与含有 1、2 或 3 个环杂原子的 5 元或 6 元环稠合的吡啶环 ;c) 与含有 1 或 2 个环杂原子的 5 元或 6 元环稠合的嘧啶环 ;d) 与含有 1、2 或 3 个环杂原子的 5 元或 6 元环稠合的吡咯环 ;e) 与含有 1 或 2 个环杂原子的 5 元或 6 元环稠合的吡唑环 ;f) 与含有 1 或 2 个环杂原子的 5 元或 6 元环稠合的咪唑环 ;g) 与含有 1 或 2 个环杂原子的 5 元或 6 元环稠合的噁唑环 ;h) 与含有 1 或 2 个环杂原子的 5 元或 6 元环稠合的异噁唑环 ;i) 与含有 1 或 2 个环杂原子的 5 元或 6 元环稠合的噻唑环 ;j) 与含有 1 或 2 个环杂原子的 5 元或 6 元环稠合的异噻唑环 ;k) 与含有 1、2 或 3 个环杂原子的 5 元或 6 元环稠合的噻吩环 ;l) 与含有 1、2 或 3 个环杂原子的 5 元或 6 元环稠合的呋喃环 ;m) 与含有 1、2 或 3 个环杂原子的 5 元或 6 元环稠合的环己基环 ;和 n) 与含有 1、2 或 3 个环杂原子的 5 元或 6 元环稠合的环戊基环。

[0109] 含有与另一个 5 元环稠合的 5 元环的双环杂芳基基团的特定示例（即 8 元稠合双环）包括但不限于咪唑并噻唑（例如，咪唑并 [2,1-b] 噻唑）和咪唑并咪唑（例如，咪唑并 [1,2-a] 咪唑）。

[0110] 含有与 5 元环稠合的 6 元环的双环杂芳基基团的特定示例（即 9 元稠合双环）包括但不限于苯并呋喃、苯并噻吩、苯并咪唑、苯并噁唑、异苯并噁唑、苯并异噁唑、苯并噻唑、苯并异噻唑、异苯并呋喃、吲哚、异吲哚、吲哚嗪、二氢吲哚、异二氢吲哚、嘌呤（例如，腺嘌

呤、鸟嘌呤）、吲唑、咪唑并吡啶（例如，咪唑并 [1,2-a] 吡啶和咪唑并 [4,5-b] 吡啶）、吡唑并嘧啶（例如，吡唑并 [1,5-a] 嘧啶）、苯并间二氧杂环戊烯和吡唑并吡啶（例如，吡唑并 [1,5-a] 吡啶）基团。与 5 元环稠合的 6 元环的另一个示例是吡咯并吡啶基团（如吡咯并 [2,3-b] 吡啶基团）。

[0111] 含有 2 个稠合 6 元环的双环杂芳基基团的特定示例（即 10 元稠合双环）包括但不限于喹啉、异喹啉、苯并二氢吡喃、二氢苯并噻喃、苯并吡喃（包括任选氧代（＝O），即氧代苯并吡喃）、异苯并吡喃、异苯并二氢吡喃、苯并二噁烷、喹嗪、苯并噁嗪、苯并二嗪、吡啶并吡啶、喹喔啉、喹唑啉、噌啉、2,3- 二氮杂萘、1,5- 二氮杂萘和蝶啶基团。

[0112] 含有芳族环和非芳族环的杂芳基基团的示例包括四氢化萘、四氢异喹啉、四氢喹啉、二氢苯并噻吩、二氢苯并呋喃、2,3- 二氢 - 苯并 [1,4] 二噁烯、苯并 [1,3] 间二氧杂环戊烯、4,5,6,7- 四氢苯并呋喃、二氢吲哚、异二氢吲哚和茚满基团。

[0113] 与碳环芳族环稠合的芳族杂环基的示例可以因此包括但不限于苯并苯硫基、吲哚基、异吲哚基、苯并呋喃基、异苯并呋喃基、苯并咪唑基、吲唑基、苯并噁唑基、苯并异噁唑基、异苯并噁唑基、苯并噻唑基、苯并异噻唑基、喹啉基、异喹啉基、喹喔啉基、喹唑啉基、噌啉基、苯并三嗪基、2,3- 二氮杂萘基、咔啉基等。

[0114] 术语“非芳族杂环基”包括任选经取代的饱和和不饱和环，其含有至少一个选自 N、S 和 O 的杂原子。

[0115] 非芳族杂环基可以是 3-7 元单环。本文所用术语“3-7 元单环”涉及具有 3、4、5、6 或 7 个环原子或包括这些整数中任意两个的范围的单环基团。5 元非芳族杂环的示例包括 2H- 吡咯基、1- 吡咯啉基、2- 吡咯啉基、3- 吡咯啉基、吡咯烷基、1- 吡咯烷基、2- 吡咯烷基、3- 吡咯烷基、四氢呋喃基、四氢苯硫基、吡唑啉基、2- 吡唑啉基、3- 吡唑啉基、吡唑烷基、2- 吡唑烷基、3- 吡唑烷基、咪唑烷基、3- 二氧杂环戊烷基 (3-dioxalanyl)、噻唑烷基、异噁唑烷基、2- 咪唑啉基等。

[0116] 6 元非芳族杂环基的示例包括哌啶基、哌啶酮基、吡喃基、二氢吡喃基、四氢吡喃基、2H 吡喃基、4H 吡喃基、噻烷基 (thianyl)、氧化噻烷基 (thianyl oxide)、二氧化噻烷基 (thianyl dioxide)、哌嗪基、二噁烷基 (diozanyl)、1,4- 二噁英基、1,4- 二噻烷基、1,3,5- 三噁烷基 (1,3,5-triozalanyl)、1,3,5- 三噻烷基、1,4- 吗啉基、硫代吗啉基、1,4- 氧硫杂环己烷基、三嗪基、1,4- 噻嗪基等。

[0117] 7 元非芳族杂环基的示例包括氮杂环庚烷基、氧杂环庚烷基、硫杂环庚烷基等。

[0118] 非芳族杂环也可以是双环杂环（如连环体系（如尿苷基 (uridinyl) 等）或稠环体系）。稠环体系包括与碳环芳族环（如苯基、萘基、茚基、蒽基、芴基、蒽基等）稠合的非芳族 5 元、6 元或 7 元杂环。与碳环芳族环稠合的非芳族 5 元、6 元或 7 元杂环的示例包括二氢吲哚基、苯并二氮杂䓬基 (benzodiazepinyl)、苯并氮杂䓬基 (benzazepinyl)、二氢苯并呋喃基等。

[0119] 术语“螺环体系”表示一种双环体系，其中环通过单个共享的原子或“螺原子”（更具体地是四级碳（“螺碳”））连接，且包括含有 1、2、3 或 4 个杂原子的螺双环 7-11 元碳环和螺双环 7-11 元杂环，所述杂原子独立地选自 O、N 和 S。

[0120] 术语“来源于氨基酸”表示可能存在于天然 (L-) 或非天然 (D-) 氨基酸中的任意侧链。来源于天然氨基酸的氨基酸侧链部分的示例（括号中显示其源自的氨基酸）

是 -H（甘氨酸）、$-CH_3$（丙氨酸）、$-CH(CH_3)_2$（缬氨酸）、$-CH_2CH(CH_3)_2$（亮氨酸）、$-CH(CH_3)CH_2CH_3$（异亮氨酸）、$-(CH_2)_4NH_2$（赖氨酸）、$-(CH_2)_3NHC(=NH)NH_2$（精氨酸）、$-CH_2-$(5-1H- 咪唑基)（组氨酸）、$-CH_2CONH_2$（天冬酰胺）、$-CH_2CH_2CONH_2$（谷氨酰胺）、$-CH_2COOH$（天冬氨酸）、$-CH_2CH_2COOH$（谷氨酸）、$-CH_2-$ 苯基（苯丙氨酸）、$-CH_2-$(4-OH- 苯基)（酪氨酸）、$-CH_2-$(3-1H- 吲哚基)（色氨酸）、$-CH_2SH$（半胱氨酸）、$-CH_2CH_2SCH_3$（甲硫氨酸）、$-CH_2OH$（丝氨酸）、$-CH(OH)CH_3$（苏氨酸）和环状侧链吡咯烷基（脯氨酸），其中吡咯烷基环中氮和碳之间的共价键形成了骨架。来源于非天然氨基酸的氨基酸侧链部分的示例（括号中显示其源自的氨基酸）是 $-(CH_2)_2-C(O)-O-C(CH_3)_3$（谷氨酸叔丁酯）、$-(CH_2)_4-NH-C(O)-O-C(CH_3)_3$（$N_\varepsilon$-（叔丁氧基羰基）-赖氨酸）、$-(CH_2)_3-NH-C(O)NH_2$（瓜氨酸）、$-CH_2-CH_2OH$（高丝氨酸）和 $-(CH_2)_2-CH_2NH_2$（鸟氨酸）。示例还可包括烷基、烯基、炔基、芳基、饱和和不饱和杂环（官能化和非官能化的）。术语“氨基酸侧链部分”也可包括一系列非天然酰胺和磺酰胺、芳基和杂芳基侧链。

[0121] 除非另外说明，本文所用术语“任选经取代的”或“任选的取代基”是指可以由或可以不由 1、2、3、4 或更多个，优选 1、2 或 3 个，更优选 1 或 2 个选自下组的基团进一步取代的基团：C_{1-6} 烷基、C_{2-6} 烯基、C_{2-6} 炔基、C_{3-8} 环烷基、羟基、氧代、C_{1-6} 烷氧基、芳氧基、C_{1-6} 烷氧基芳基、卤素、C_{1-6} 烷基卤代（如 CF_3 和 CHF_2）、C_{1-6} 烷氧基卤代（如 OCF_3 和 $OCHF_2$）、羧酸、羧基、酯、氰基、硝基、氨基、单取代氨基、双取代氨基、酰基、酮、酰胺、氨酰基、取代的酰胺、双取代的酰胺、氨基甲酸、氨基甲酸酯、巯基、烷基硫代、硫代、硫酸、磺酸、亚磺酰基、取代的亚磺酰基、磺酰基、取代的磺酰基、磺酰胺、取代的磺酰胺、双取代的磺酰胺、磷酸、膦酸、芳基、芳基 C_{1-6} 烷基、杂环基、杂芳基和螺环体系，其中各烷基、烯基、炔基、环烷基、芳基、杂环基、杂芳基和螺环体系以及含有它们的基团可以被进一步任选地取代。除非另外说明，本发明的一个实施方式中特别优选的任选的取代基包括 1、2、3 或 4 个，优选 1 或 2 个选自以下组的取代基：C_{1-4} 烷基（特别是甲烷）、卤素（特别是氟）、卤代 C_{1-3} 烷基（特别是 CHF_2 和 CF_3）、OH、C_{1-4} 烷氧基（特别是 OCH_3）、CO_2H、CO_2C_{1-4} 烷基（特别是 CO_2CH_3）、NH_2、NHC_{1-4} 烷基（特别是 $NHCH_3$）、$N(C_{1-4}$ 烷基$)_2$（特别是 $N(CH_3)_2$）、$NHC(=O)C_{1-4}$ 烷基、NHC(=O)-4-6 元杂环基、$OP(=O)(OR)_2$（其中各 R 独立地是 H 或 C_{1-4} 烷基）、$P(=O)(OR)_2$（其中各 R 独立地是 H 或 C_{1-4} 烷基）、C_{3-6} 环烷基（特别是环丙烷基、环丁烷基、环戊烷基和环己烷基）、苯基、4-6 元杂环基（特别是氧杂环丁基、吖丁啶基、四氢呋喃基、吡咯烷基、四氢吡喃基、吗啉基、硫代吗啉基、氧杂噻嗪基、二氧杂噻嗪基、噻烷基（也称作四氢噻喃基）、氧杂噻烷基、二氧杂噻烷基、哌啶基和哌嗪基），此外单独或作为取代基的一部分的 C_{1-4} 烷基包括甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基和叔丁基并可进一步任选地取代。

[0122] 在含 N 的杂环、杂芳基和螺双环杂环体系的情况下，任选的取代基还可以包括但不限于烷基（即 N-C_{1-3} 烷基），更优选甲基，尤其是 N- 甲基。

[0123] 应理解含有氮的芳族杂环的合适衍生物包括其 N- 氧化物。

[0124] 现在通过以下非限制性实施例描述实施方式。

[0125] 化合物

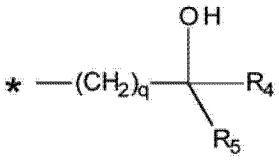
[0126] 在一个实施方式中，Alk 是任选经取代的 C_{1-6} 烷基，优选是 C_{1-3} 烷基且更优选是未经取代的乙基。

[0127] 在一个实施方式中，X_1 是 C-R_1、X_2 是 C-R_2 且 X_3 是 C-R_3。

[0128] 在一个实施方式中，X_1 是 C-R_1 且 R_1 是 H 或卤素，优选 H。

[0129] 在一个实施方式中，环 A 是任选经取代的 5-6 元杂芳基，优选包含至少一个 N 杂原子。在一个实施方式中，环 A 是 5 元杂芳基。优选的 5 元杂芳基包括三唑基、咪唑基和噻唑基环。在一个实施方式中，环 A 是 6 元杂芳基，最优选嘧啶、吡啶和吡嗪环。

[0130] 在一个实施方式中，Z_1 是通式

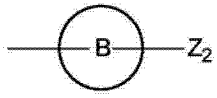
[0131] 

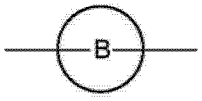
的仲或叔醇、其酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯或前药，其中 q、R_4 和 R_5 如前文所定义。

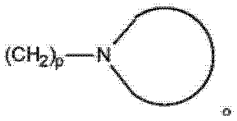
[0132] 在一个实施方式中，X_2 是 C-R_2，其中 R_2 是 H。在另一个实施方式中，X_2 是 C-R_2，其中 R_2 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 OC_{1-6} 烷基、任选经取代的 SC_{1-6} 烷基、任选经取代的 S(＝O)C_{1-6} 烷基、任选经取代的 5-6 元杂环、卤素、卤代 C_{1-3} 烷基、CN 和任选经取代的 $(CH_2)_mNR^aR^b$。

[0133] 在一个实施方式中，R_2 选自 H、卤素（优选 F）、OH、任选经取代的 NHC_{1-3} 烷基（优选 $NHCH_3$ 或 $NHCH_2CH_3$）、任选经取代的 $N(C_{1-3}$ 烷基$)_2$（优选 $N(CH_3)_2$ 或 $N(CH_3)CH_2CH_3$）、任选经取代的 SC_{1-3} 烷基（优选 SCH_2CH_3）、任选经取代的 S(＝O)C_{1-3} 烷基（优选 S(＝O)CH_2CH_3）、任选经取代的 6 元杂环（优选 6 元如吗啉）和任选经取代的 OC_{1-3} 烷基（优选甲氧基或乙氧基），其中任选的取代基可以是例如 OH、甲氧基、C_{3-6} 环烷基（例如环丙基）、苯基或 5-6 元杂环（例如四氢呋喃、四氢吡喃、吡咯烷、吡唑烷、吡唑啉、哌啶、哌嗪和吗啉）。

[0134] 在一个实施方式中，X_3 是 C-R_3，其中 R_3 是 H。

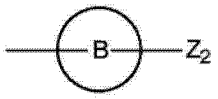
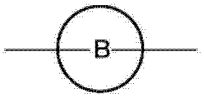
[0135] 在另一个实施方式中，X_3 是 C-R_3，其中 R_3 选自任选经取代的 C_{1-6} 烷基、任选经取代的 $CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mNR^aR^b$ 或是式 

的基团，其中＊表示与碳环原子的连接点； 

表示环 B，其选自饱和或不饱和的单环 3-7 元杂环、饱和或不饱和的稠合双环 8-10 元杂环、C_{6-10} 芳基和 5-10 元杂芳基并可被任选地取代；Z_2 是仲或叔醇，或者 Z_2 选自 H、OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mNR^aR^b$、任选经取代的 $(CH_2)_p$-4-6 元杂环、任选经取代的 $(CH_2)_p$- 螺 - 双环 -7-11 元杂环和任选经取代的 

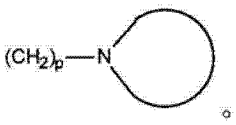
。

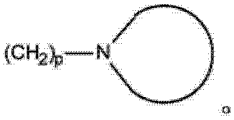
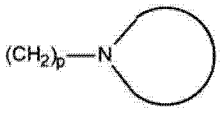
[0136] 在另一个实施方式中，R_3 选自任选经取代的 C_{1-3} 烷基、任选经取代的 OC_{1-3} 烷基、任选经取代的 $(CH_2)_mNH_2$、任选经取代的 $(CH_2)_mNHC_{1-3}$ 烷基和任选经取代的 $(CH_2)_mN(C_{1-3}$ 烷基$)_2$。在另一个实施方式中，R_3 选自任选经取代的甲基（如任选地被甲氧基、二甲基氨基或 6 元杂环基（如吗啉基）取代）或任选经取代的甲氧基（如任选地被吡啶基取代，其中吡啶基进一步任选地被甲基取代）。

[0137] 在另一个实施方式中，R_3 是式  的基团，其中 * 表示与碳环原子的连接点；  表示环 B，其选自饱和或不饱和的单环 5-6 元杂环（如吡咯烷基 (pyrrolindinyl) 和吗啉基）、C_6 芳基和 5-6 元杂芳基并可被任选地取代。

[0138] 在一个优选实施方式中，环 B 是任选经取代的 5-6 元杂芳基、特别优选 6 元杂芳基且选自吡啶、哒嗪、嘧啶和吡嗪的 6 元杂芳基是最优选的。

[0139] 在一个实施方式中，Z_2 是 H。

[0140] 在一个实施方式中，Z_2 选自 OH、任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基、$(CH_2)_mNH_2$、任选经取代的 $(CH_2)_mNHC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mN(C_{1-6}$ 烷基$)_2$、任选经取代的 $(CH_2)_p$-4-6 元杂环、任选经取代的 $(CH_2)_p$- 螺 - 双环 -7-11 元杂环和任选经取代的  。

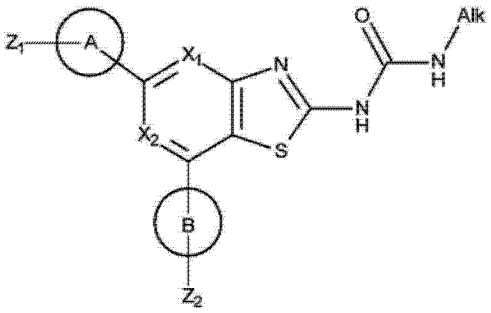
[0141] 在另一个实施方式中，Z_2 选自 OH、卤素（优选 F）、任选经取代的 C_{1-6} 烷基（特别是甲基、乙基和丙基，最优选甲基）、任选经取代的 OC_{1-6} 烷基（特别是甲氧基、乙氧基和丙氧基）、卤素（优选 F）、$(CH_2)_mNH_2$（特别是 NH_2）、任选经取代的 $(CH_2)_mNHC_{1-3}$ 烷基（特别是 $NHCH_3$ 和 $NHCH_2CH_3$）、任选经取代的 $(CH_2)_mNHC_{3-6}$ 环烷基（特别是 CH_2NHC_{3-6} 环烷基（如 CH_2NH 环丙烷基）和 NHC_{3-6} 环烷基（如 NH- 环已烷基）、任选经取代的 $(CH_2)_mN(C_{1-3}$ 烷基$)_2$（特别是 $N(CH_3)_2$ 和 $N(CH_3)CH_2CH_3$）、任选经取代的 $(CH_2)_p$-4-6 元杂环、任选经取代的 $(CH_2)_p$- 螺 - 双环 -7-11 元杂环和任选经取代的  。在另一个实施方式中，Z_2 是任选经取代的  ，其中 p 是 0、1 或 2，优选 0 或 1，更优选是 1。

[0142] 在一个特别优选的实施方式中，Z_2 是任选经取代的 $(CH_2)_p$-4-6 元杂环或任选经取代的 $(CH_2)_p$- 螺 - 双环 -7-11 元杂环，其中 p 是选自 0、1 或 2 的整数，优选 0 或 1。特别优选的 4-6 元杂环包含至少一个氮杂原子且包括吖丁啶基、吡咯烷基、哌啶基、哌嗪基、吗啉基、硫代吗啉基、氧杂噻嗪基和二氧杂噻嗪基，并可进一步被任选地取代。特别优选的螺 - 双环 -7-11 元杂环包括氧杂氮杂螺庚烷和氧杂氮杂螺壬烷并可被任选地取代。

[0143] 合适的 Z_2 的任选取代基包括但不限于一种或多种取代基，优选的 1 或 2 种取代基独立地选自 OH、C_{1-3} 烷基（特别是甲基）、C_{1-3} 烷氧基（特别是甲氧基）、卤素（特别是 F）、CO_2H、CO_2C_{1-3} 烷基（特别是 CO_2CH_3）、$P(=O)(OH)_2$ 和 $P(=O)(OC_{1-3}$ 烷基$)_2$。

[0144] 在一个实施方式中，所述化合物是式 (Ia)

[0145]

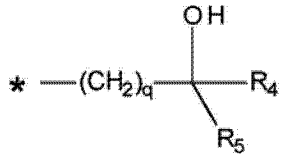


(Ia)

[0146] 其盐、异构体、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药。

[0147] 其中 X_1、X_2、Alk、环 A、环 B、Z_1 和 Z_2 如前文所定义。

[0148] 在一个实施方式中，Z_1 是通式

[0149]  的仲或叔醇，或其酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯或前药。

[0150] 其中 q 是选自 0、1、2 和 3 的整数并且各 (CH_2) 实体（存在时）可独立地被任选取代；

[0151] R_4 是 H 或选自任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 $(CH_2)_tOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tOC(=O)C_{1-6}$ 烷基、任选经取代的 $(CH_2)_tSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基和任选经取代的 $(CH_2)_tNR^aR^b$；

[0152] R_5 选自任选经取代的 C_{1-6} 烷基、任选经取代的 C_{2-6} 烯基、任选经取代的 C_{2-6} 炔基、任选经取代的 C_{3-7} 环烷基环、任选经取代的苯基、任选经取代的 4-6 元杂环、任选经取代的 5-6 元杂芳环、任选经取代的 $(CH_2)_tOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tOC(=O)C_{1-6}$ 烷基、任选经取代的 $(CH_2)_tSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_tOC(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基和任选经取代的 $(CH_2)_tNR^aR^b$；

[0153] t 选自 1、2、3、4、5 和 6 且优选为 1、2 或 3。

[0154] R^a 和 R^b 各独立地选自 H 或任选经取代的 C_{1-6} 烷基；

[0155] 或 R_4 和 R_5 与其连接的碳原子形成任选经取代的 4-6 元杂环或 C_{3-7} 环烷基环；以及

[0156] * 表示与环 A 连接的点。

[0157] 在一个实施方式中，q 是 0 或 1，优选是 0。

[0158] 在一个实施方式中，R_4 是 H 或任选经取代的 C_{1-3} 烷基（特别是甲基和乙基）；R_5 选自任选经取代的 C_{1-3} 烷基（特别是甲基和乙基）、任选经取代的卤代 C_{1-3} 烷基（特别是 CHF_2、CH_2CHF_2、CF_3 和 CH_2CF_3）、任选经取代的 C_{3-7} 环烷基环（特别是环丙基、环丁基、环戊基和环己基）、任选经取代的 4-6 元杂环（特别是吗啉基）、任选经取代的 5-6 元杂环（特别是包含至少一个氮杂原子（如咪唑基和吡啶基））；或 R_4 和 R_5 与其连接的碳原子形成任选经取代的 4-6 元杂环或 C_{3-6} 环烷基环。

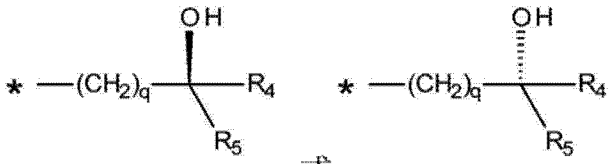
[0159] R_4 和 R_5 与其连接的碳原子所形成的 4-6 元杂环包括 4 元环（如氧杂环丁烷和氮杂环丁烷）、5 元环（如吡咯烷、吡唑烷、咪唑、四氢呋喃和噻吩）和 6 元环（如哌啶、哌嗪、吗啉、四氢吡喃和四氢噻喃）。就杂环而言，杂原子环取代基包括＝ O（例如 S ＝ O，例如由四氢噻喃形成氧代 - 硫杂环戊烷 (oxo-thiane) 或二氧代硫杂环戊烷 (dioxo-thiane))、氧化物（例如 N- 氧化物）和 C_{1-3} 烷基（例如 N- 甲基）。

[0160] R_4 和 R_5 与其连接的碳原子所形成的 C_{3-6} 环烷基环包括饱和的环丙基、环丁基、环戊基和环己基环，特别是环戊基和环己基。

[0161] 合适的 R_4 和 R_5 的任选的取代基包括但不限于例如一个或多个，优选 1 或 2 个取代基，其独立地选自 OH、C_{1-3} 烷基（如甲基）、卤代 C_{1-3} 烷基（如 CHF_2 和 CF_3）、CO_2H、CO_2C_{1-4} 烷基、C_{1-3} 烷氧基（如甲氧基）、氧代（＝ O）、NH_2、NHC_{1-3} 烷基和 $N(C_{1-3}$ 烷基 $)_2$。

[0162] 在另一个实施方式中，Z_1 或 Z_2（优选 Z_1）是通式

[0163]



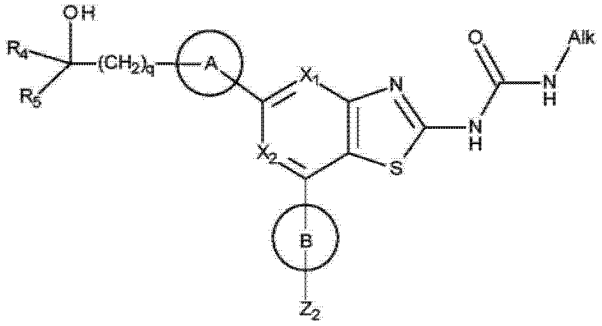
或

[0164] 的手性醇或其酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯或前药，其中 q、R_4、R_5 和 * 如前文所定义，前提是 R_4 和 R_5 是不同的。在一个优选实施方式中，q 是 0 或 1，优选是 0。

[0165] 在一个实施方式中，当 Z_1 是手性醇时，如前文所定义的式 (I) 或 (Ia) 的化合物可以其外消旋混合物、单个对映异构体和 / 或混合物的形式存在。

[0166] 在一个实施方式中，所述化合物是式 (II)：

[0167]



(II)

[0168] 其盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药。

[0169] 其中 X_1、X_2、Alk、环 A、环 B、Z_2、R_4、R_5 和 q 如前文所定义。在一个优选实施方式中，q 是 0 或 1，优选是 0。

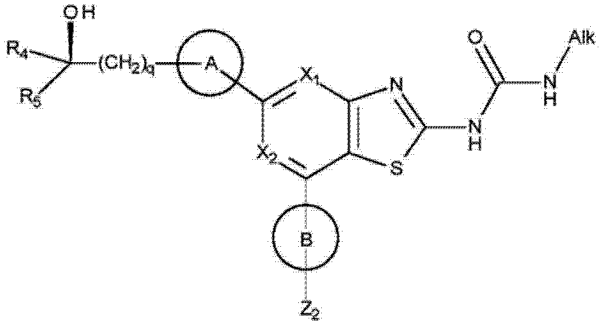
[0170] 在一个优选实施方式中，X_1 是 C-H，q 是 0 或 1，优选是 0 且 Alk 是乙基。

[0171] 在另一个实施方式中，R_4 是 H 或任选经取代的 C_{1-6} 烷基且 R_5 是任选经取代的 C_{1-6} 烷基。在另一个更特别的实施方式中，R_4 是 H 或任选经取代的甲基、乙基或丙基且 R_5 是任

选经取代的甲基、乙基或丙基。

[0172] 在一个实施方式中，式（II）的化合物以式（IIa）的单个对映异构体的形式存在：

[0173]



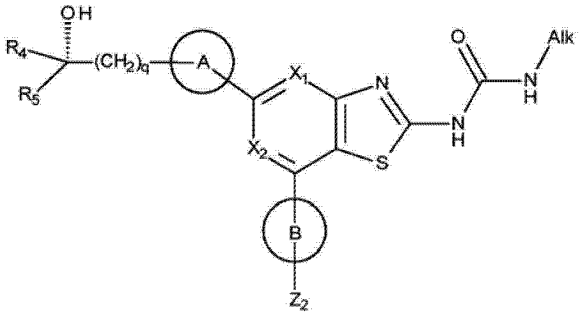
(IIa)

[0174] 其盐、酯、氨基甲酸盐／酯、磷酸盐／酯、硫酸盐／酯、氘代形式和前药。

[0175] 其中 X_1、X_2、Alk、环 A、环 B、Z_2、R_4、R_5 和 q 如前文所定义，前提是 R_4 和 R_5 是不同的。在一个优选实施方式中，q 是 0 或 1，优选是 0。

[0176] 在另一个实施方式中，式（II）的化合物以式（IIb）的单个对映异构体的形式存在：

[0177]



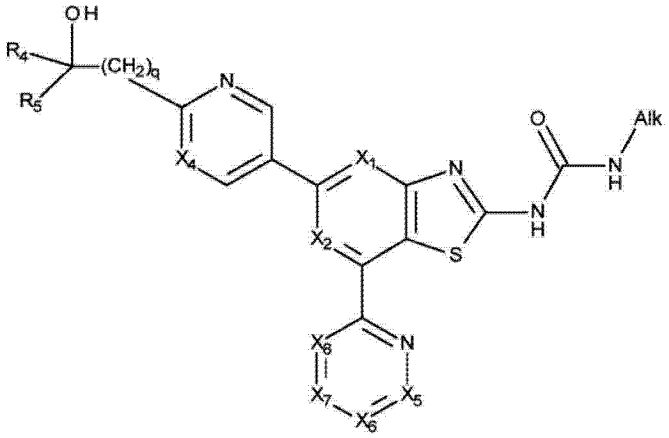
(IIb)

[0178] 其盐、酯、氨基甲酸盐／酯、磷酸盐／酯、硫酸盐／酯、氘代形式和前药。

[0179] 其中 X_1、X_2、Alk、环 A、环 B、Z_2、R_4、R_5 和 q 如前文所定义，前提是 R_4 和 R_5 是不同的。在一个优选实施方式中，q 是 0 或 1，优选是 0。

[0180] 在一个实施方式中，所述化合物是式（III）

[0181]



(III)

[0182] 其盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯、氘代形式和前药。

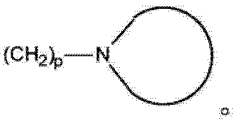
[0183] 其中 X_1、X_2、Alk、R_4、R_5 和 q 如前文所定义；

[0184] X_4 是 N、CH、C- 卤素或 C-C_{1-3} 烷氧基，优选是 N 或 CH；

[0185] X_5、X_6、X_7 和 X_8 各独立地选自 N、C-H 或 C-Z_2，其中 Z_2 如前文所定义，前提是 X_5、X_6、X_7 或 X_8 中不超过一个是 N。

[0186] 在一个优选实施方式中，X_1 是 C-H，q 是 0 或 1，优选是 0 且 Alk 是乙基。

[0187] 在一个实施方式中，X_5、X_6、X_7 或 X_8 中的任意一个是 C-Z_2，其中 Z_2 选自 OH、任选经取代的 C_{1-6} 烷基、任选经取代的 $(CH_2)_mOC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mSC_{1-6}$ 烷基、任选经取代的 $(CH_2)_mS(=O)C_{1-6}$ 烷基、卤素、任选经取代的卤代 C_{1-3} 烷基、任选经取代的 $(CH_2)_mNR^aR^b$、任选经取代的 $(CH_2)_p$-4-6 元杂环、任选经取代的 $(CH_2)_p$- 螺 - 双环 -7-11 元杂环和任选经取代的



[0188] 在一个实施方式中，X_5、X_6、X_7 和 X_8 各独立地是 C-H 或 C-Z_2。

[0189] 在另一个实施方式中，X_5、X_6、X_7 和 X_8 之一是 N 且剩余三个各独立地选自 C-H 或 C-Z_2。

[0190] 在另一个实施方式中，R_4 是 H 或任选经取代的 C_{1-6} 烷基且 R_5 是任选经取代的 C_{1-6} 烷基。在另一个更特别的实施方式中，R_4 是 H 或任选经取代的甲基、乙基或丙基且 R_5 是任选经取代的甲基、乙基或丙基。

[0191] 在式 (I)、(Ia)、(II)、(IIa)、(IIb) 或 (III) 中任意一个的化合物的一个实施方式中，Z_1 和 / 或 Z_2 仲或叔醇是以包括来源于氨基酸和二肽的酯、氨基甲酸盐 / 酯、磷酸盐 / 酯或硫酸盐 / 酯的形式存在。

[0192] 在式 (I)、(Ia)、(II)、(IIa)、(IIb) 或 (III) 中任意一个的化合物的一个实施方式中，Z_1 和 / 或 Z_2 仲或叔醇的酯具有通式 $OC(=O)R_6$，其中 R_6 是 5-6 元杂环或任选经取代的 C_{1-6} 烷基，其中任选的取代基独立地选自 1、2、3 或 4 个部分，所述部分选自 C_{1-3} 烷基、C_{1-3} 烷氧基、OH、OC_{1-3} 烷基、CO_2H、CO_2C_{1-3} 烷基、任选经取代的 5-6 元杂环、$NHC(O)C_{1-6}$ 烷基、NHC(O)-5-6 元杂环、$C(O)NHC_{1-6}$ 烷基、NH_2，NHC_{1-3} 烷基和 $N(C_{1-3}$ 烷基 $)_2$，其中 $NHC(O)C_{1-6}$ 烷基、

C(O)NHC_{1-6}烷基、NHC_{1-3}烷基和 N(C_{1-3}烷基)$_2$可进一步被例如 CO_2H、CO_2CH_3、5-6 元杂环、NH_2、NHC_{1-3}烷基和 N(C_{1-3}烷基)$_2$和 OP(=O)(OR_9)$_2$任选地取代，各 R_9 独立地选自 H 或 C_{1-3}烷基。优选的 5-6 元杂环包括任选经取代的吗啉基和任选经取代的吡咯烷、吡唑烷、吡唑啉、哌啶和哌嗪（如 N- 甲基哌嗪）。在一个特定实施方式中，提供了 Z_1 和 / 或 Z_2 仲或叔醇的琥珀酸酯。

[0193] 在另一个实施方式中，提供了 Z_1 和 / 或 Z_2 仲或叔醇的酯，所述酯来源于氨基酸或二肽部分。

[0194] 在式 (I)、(Ia)、(II)、(IIa)、(IIb) 或 (III) 中任意一个的化合物的一个实施方式中，Z_1 和 / 或 Z_2 仲或叔醇的氨基甲酸酯具有通式 OC(=O)NR_7R_8，其中 R_7 和 R_8 各独立地选自 H 和任选经取代的 C_{1-6}烷基或与其连接的 N 结合在一起以形成任选经取代的 5-6 元杂环。优选的 5-6 元杂环包括任选经取代的吗啉基和任选经取代的吡咯烷、吡唑烷、吡唑啉、哌啶和哌嗪（如 N- 甲基哌嗪）。

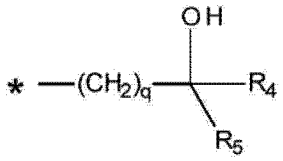
[0195] 在式 (I)、(Ia)、(II)、(IIa)、(IIb) 或 (III) 中任意一个的化合物的另一个实施方式中，Z_1 和 / 或 Z_2 仲或叔醇的磷酸盐 / 酯具有通式 OP(O)(OR_9)$_2$，其中各 R_9 独立地选自 H 或任选经取代的 C_{1-6}烷基。

[0196] 在式 (I)、(Ia)、(II)、(IIa)、(IIb) 或 (III) 中任意一个的化合物的另一个实施方式中，Z_1 和 / 或 Z_2 仲或叔醇的硫酸盐 / 酯具有通式 OSO_2OR_{10}，其中各 R_{10} 独立地选自 H 或任选经取代的 C_{1-6}烷基。

[0197] 在式 (I)、(Ia)、(II)、(IIa)、(IIb) 或 (III) 中任意一个的化合物的一个实施方式中，所述前药选自由前文所定义的仲或叔醇的羟基部分形成的酯、氨基甲酸盐 / 酯、磷酸盐 / 酯或硫酸盐 / 酯。

[0198] 在式 (I)、(Ia)、(II)、(IIa)、(IIb) 或 (III) 中任意一个的化合物的一个特别优选实施方式中，Z_1 是通式

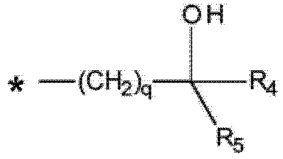
[0199]



[0200] 的仲或叔醇或其如前文所定义的酯或磷酸盐 / 酯。

[0201] 因此，在式 (I)、(Ia)、(II)、(IIa)、(IIb) 或 (III) 中任意一个的化合物的一个特别优选实施方式中，提供了具有以下通式的 Z_1 仲或叔醇的酯：

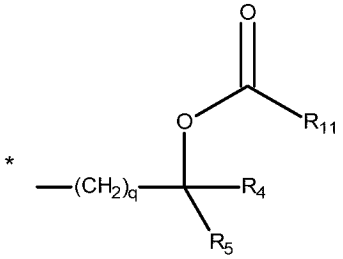
[0202]



[0203] 所述酯来源于氨基酸、多肽、氨基甲酸盐 / 酯、磷酸盐 / 酯或硫酸盐 / 酯。

[0204] 在式 (I)、(Ia)、(II)、(IIa)、(IIb) 或 (III) 中任意一个的化合物的一个实施方式中，提供了具有以下通式的 Z_1 仲或叔醇的酯：

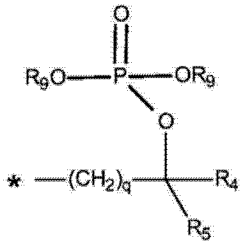
[0205]



[0206] 其中 R_{11} 是 R_6 或 NR_7R_8，R_6、R_7、R_8、q、R_4 和 R_5 如前文所定义。在一个实施方式中，R_{11} 选自由任选经取代的 5-6 元杂环基或任选经取代的 C_{1-6} 烷基组成的组。特别优选的 5-6 元杂环基包括吡咯烷基、吗啉基和哌嗪基并可被 C_{1-3} 烷基（优选甲基）任选取代。在一个实施方式中，R_{11} 是任选经取代的 C_{1-6} 烷基，其中特别优选的可选取代基独立地选自甲基、甲氧基、OH、CO_2H、CO_2C_{1-3} 烷基（特别是 CO_2CH_3）、任选经取代的 5-6 元杂环、NHC(＝O)-5-6 元杂环、NH_2、NHC_{1-3} 烷基和 $N(C_{1-3}$ 烷基$)_2$（特别是 $N(CH_3)_2$），其中 NHC_{1-3} 烷基可进一步任选地被 NH_2、CO_2H、CO_2CH_3、5-6 元杂环和 $OP(=O)(OR_9)_2$ 取代，各 R_9 独立地选自 H 或 C_{1-3} 烷基，其中特别优选的 5-6 元杂环包括吡咯烷基、哌嗪基和吗啉基。

[0207] 在式 (I)、(Ia)、(II)、(IIa)、(IIb) 或 (III) 中任意一个的化合物的另一个实施方式中，提供了具有以下通式的 Z_1 仲或叔醇的磷酸酯：

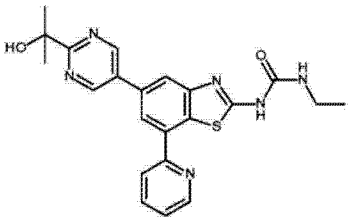
[0208]



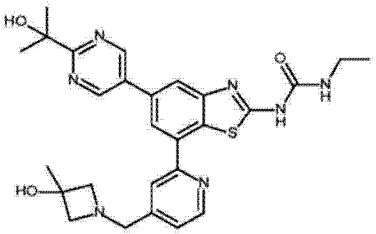
[0209] 各 R_9 独立地选自 H 或任选经取代的 C_{1-3} 烷基，且 q、R_4 和 R_5 如前文所定义。在一个实施方式中，各 R_9 是 H。

[0210] 在一个实施方式中，所述化合物选自由化合物 1 至 202 中任意一个组成的组：

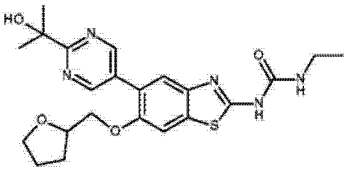
[0211]



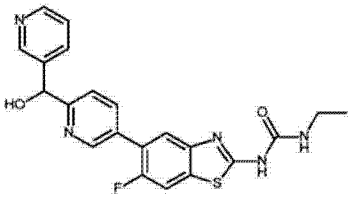
1；



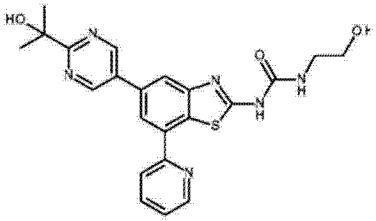
2；



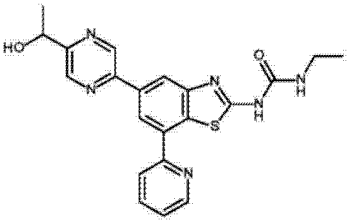
3；



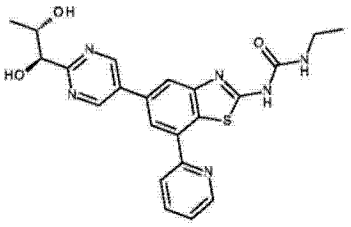
4；



5；

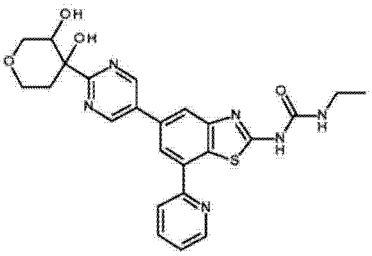


6；

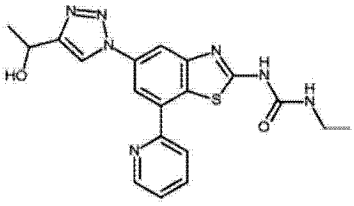


（混合物反式二醇）

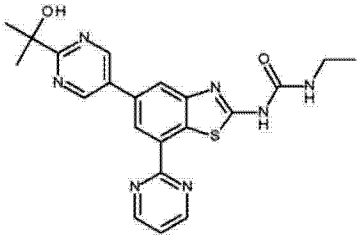
7；



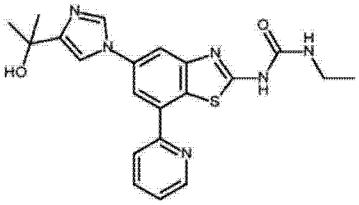
8；



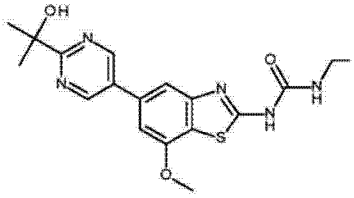
9；



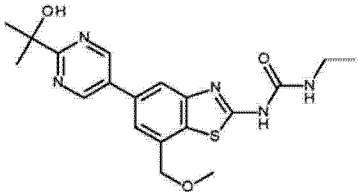
10；



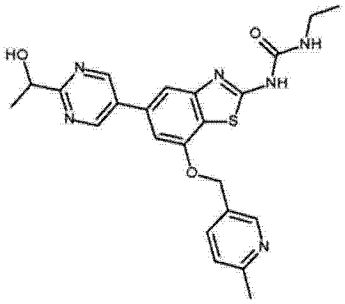
11；



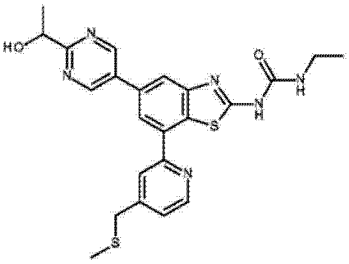
12；



13；

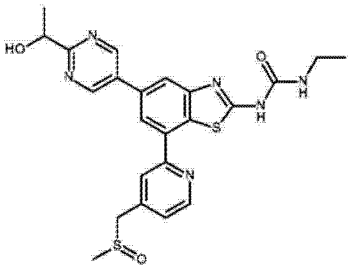


14；

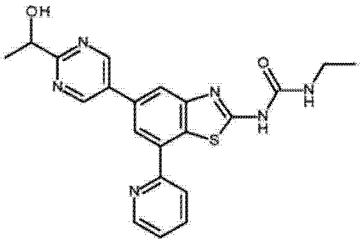


15；

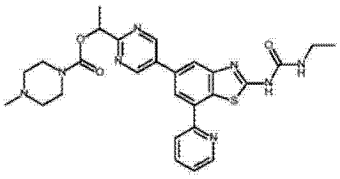
[0212]



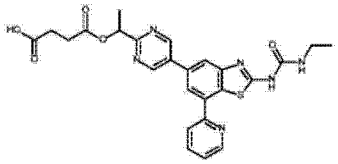
16；



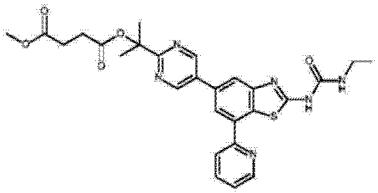
17；



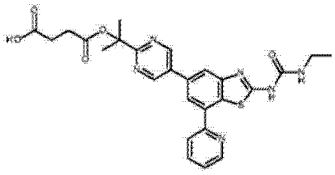
18；



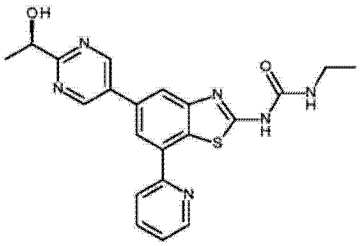
19；



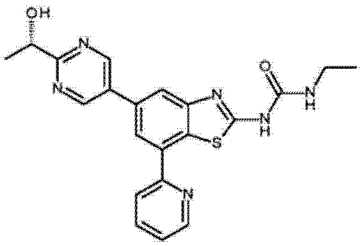
20；



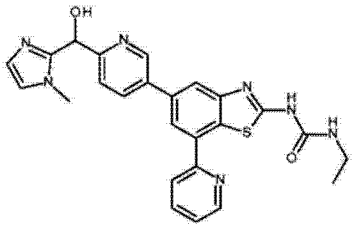
21；



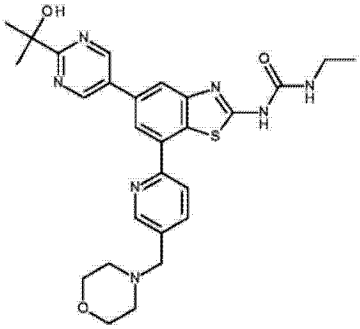
22；



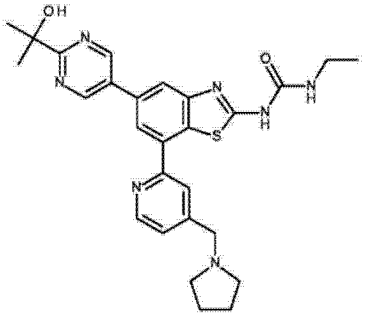
23；



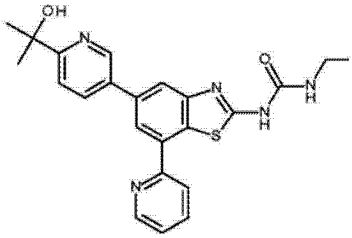
24；



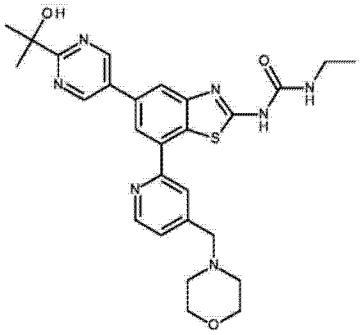
25；



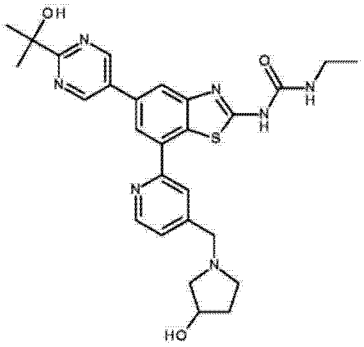
26；



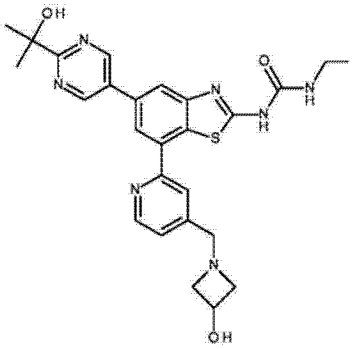
27；



28；

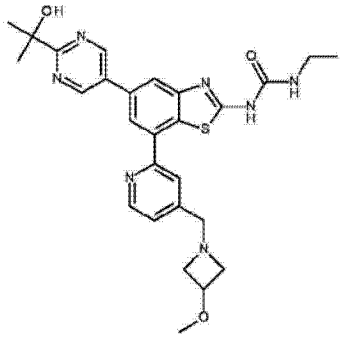


29；

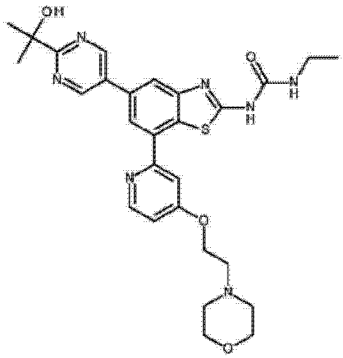


30；

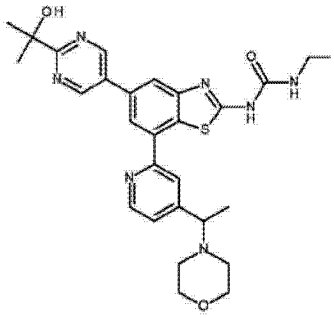
[0213]



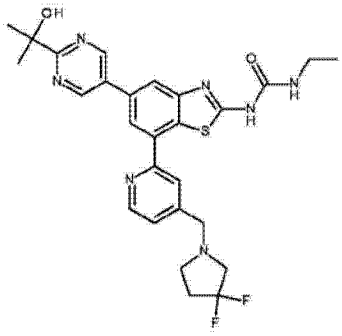
31；



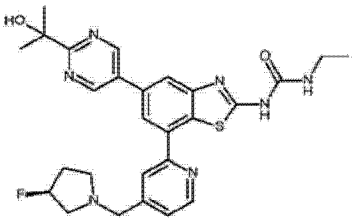
32；



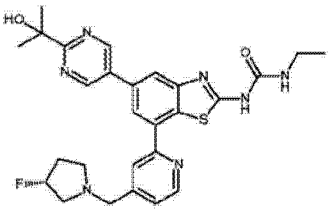
33；



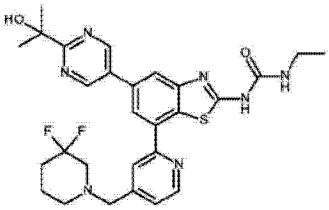
34；



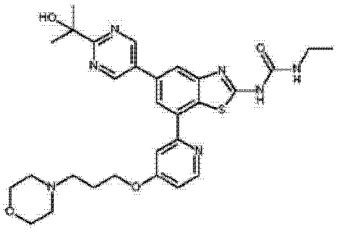
35；



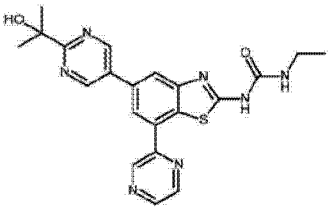
36；



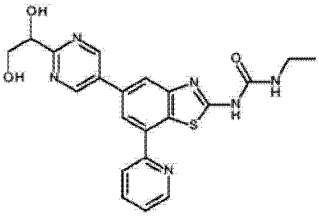
37；



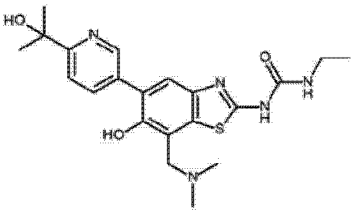
38；



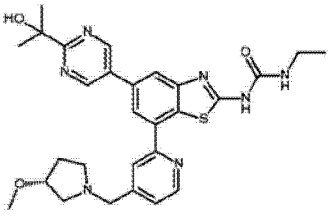
39；



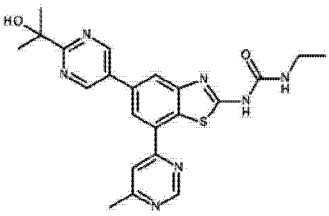
40；



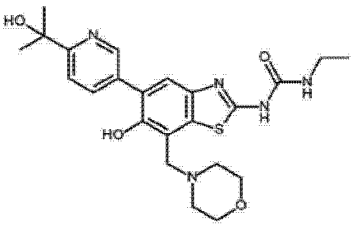
41；



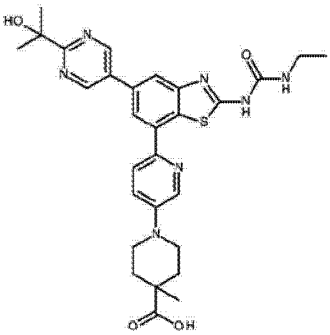
42；



43；

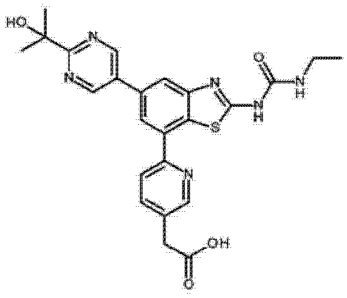


44；

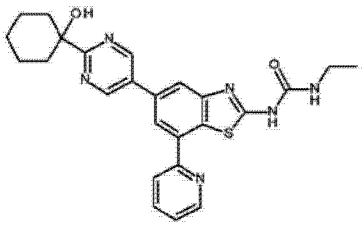


45；

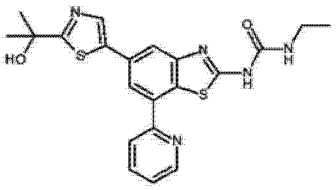
[0214]



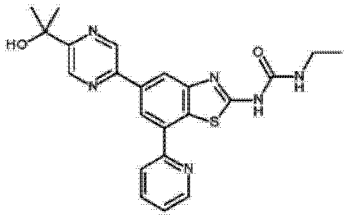
46；



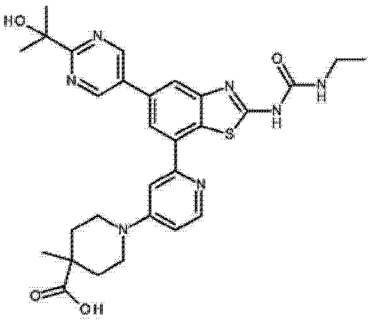
47；



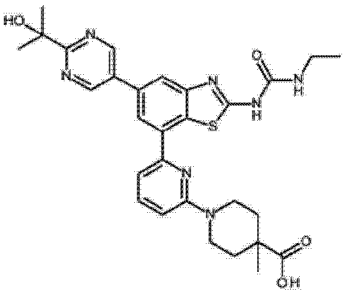
48；



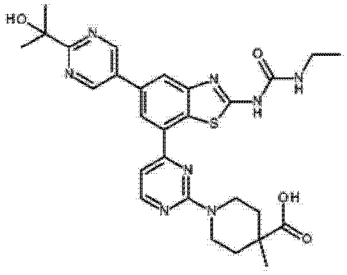
49；



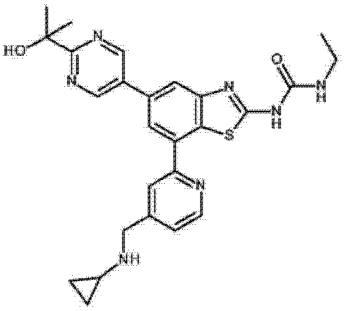
50；



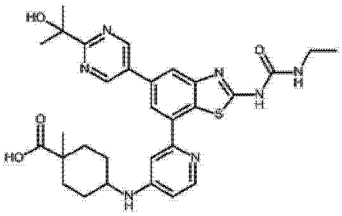
51；



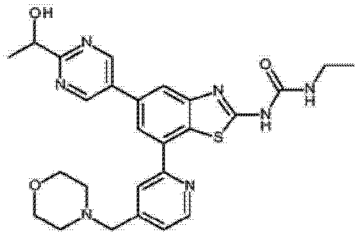
52；



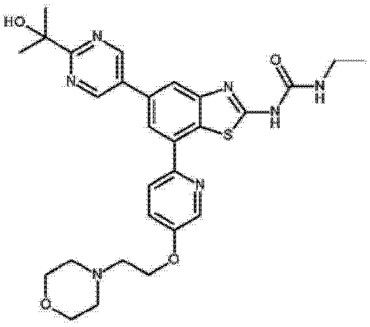
53；



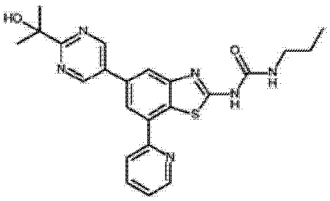
54；



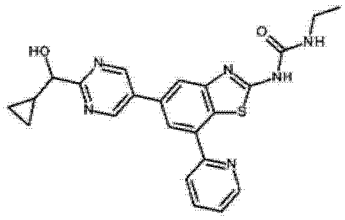
55；



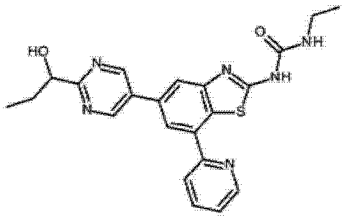
56；



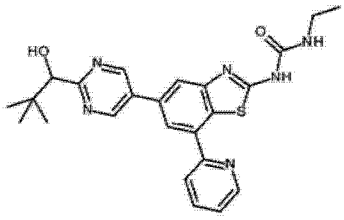
57；



58；

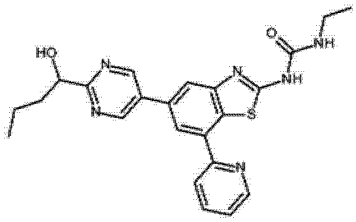


59；

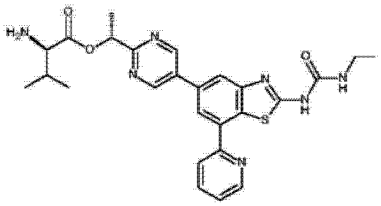


60；

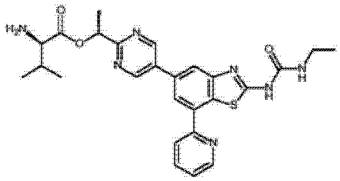
[0215]



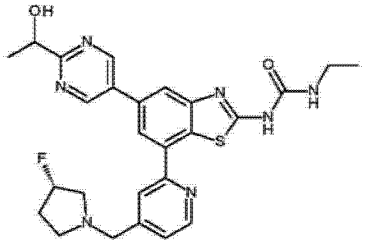
61；



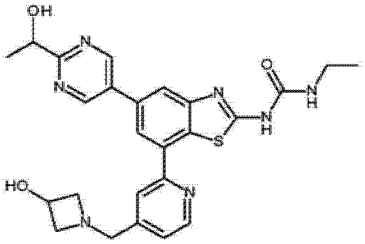
62；



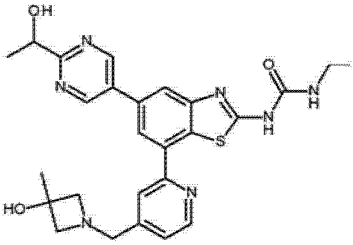
63；



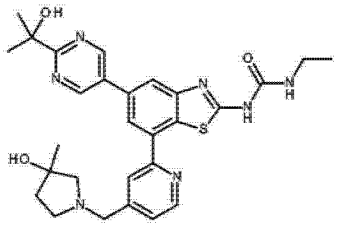
64；



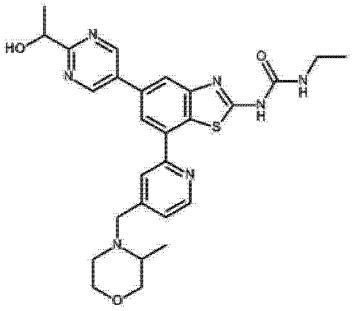
65；



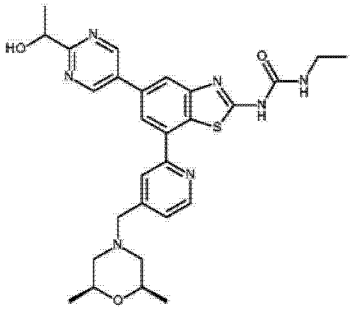
66；



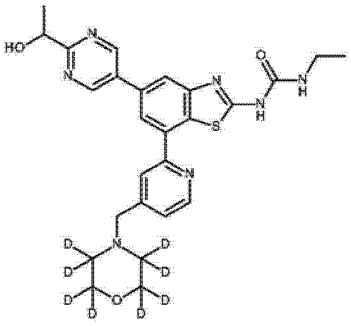
67；



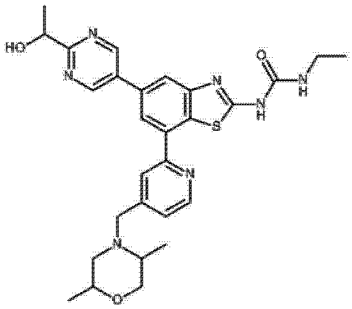
68；



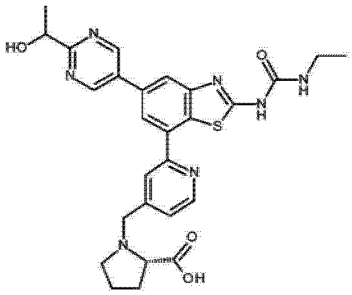
69；



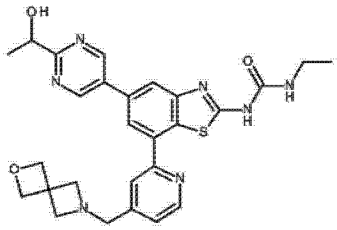
70；



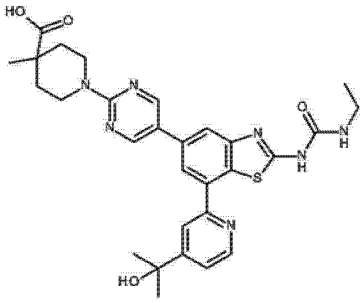
71；



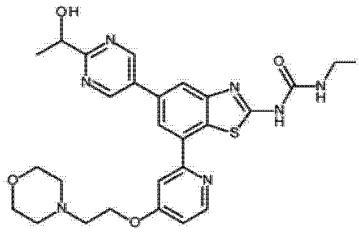
72；



73；

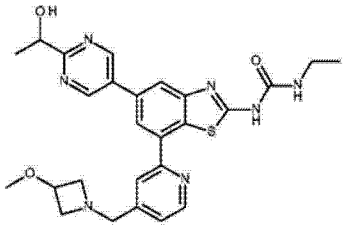


74；

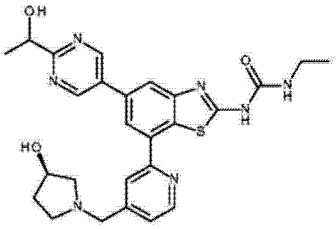


75；

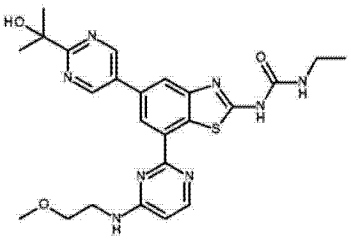
[0216]



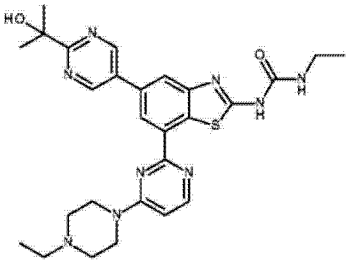
76；



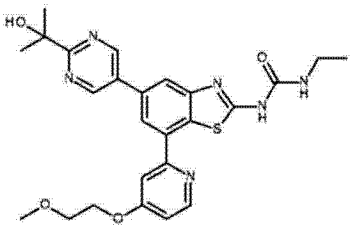
77；



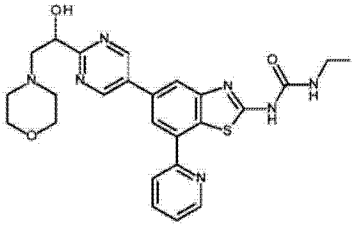
78；



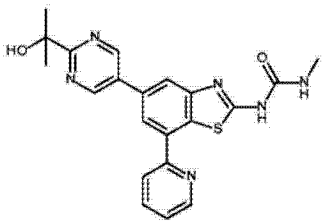
79；



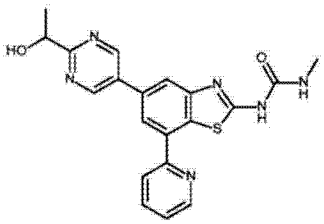
80；



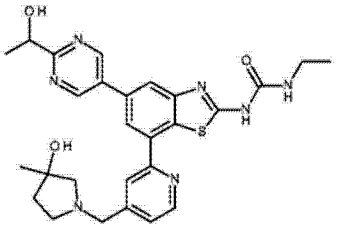
81；



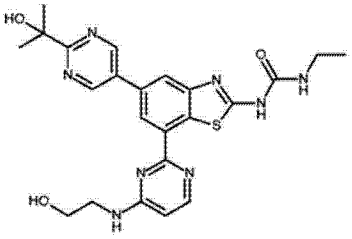
82；



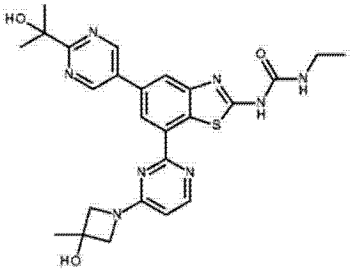
83；



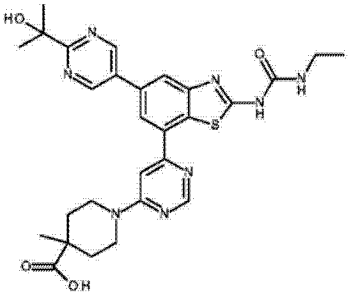
84；



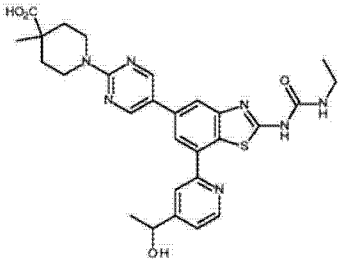
85；



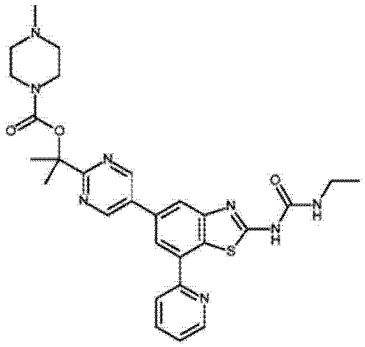
86；



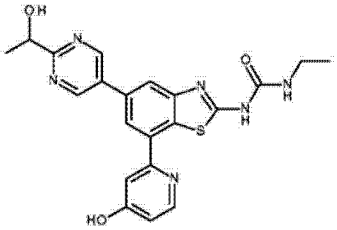
87；



88；

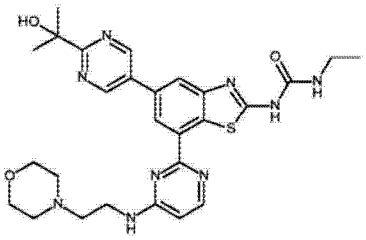


89；

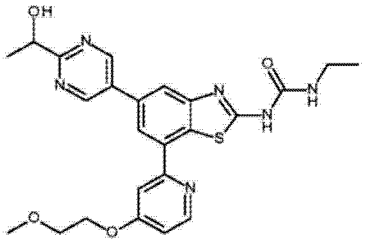


90；

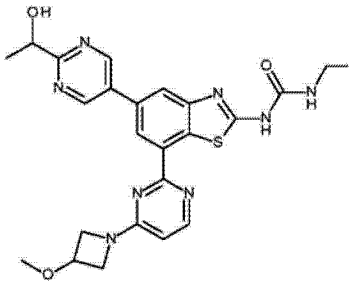
[0217]



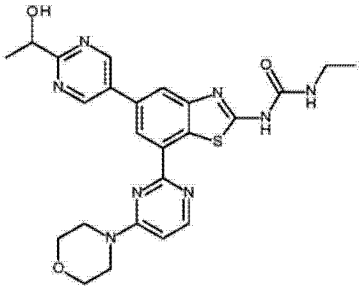
91；



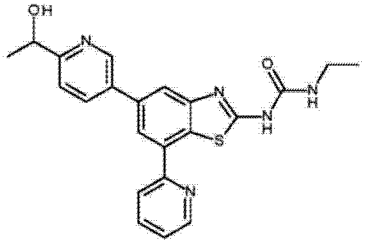
92；



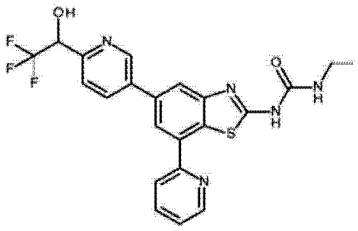
93；



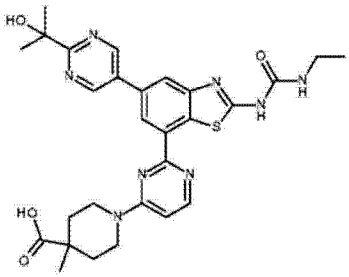
94；



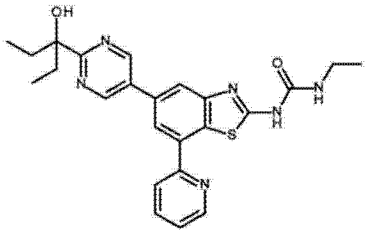
95；



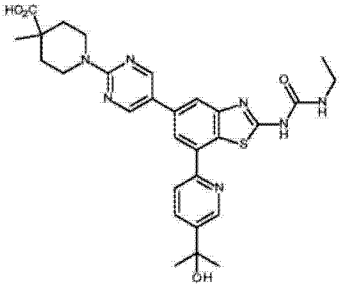
96；



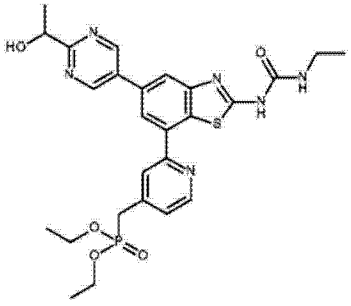
97；



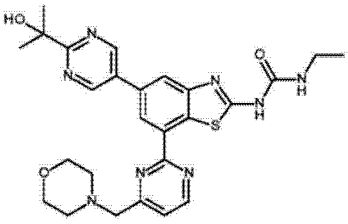
98；



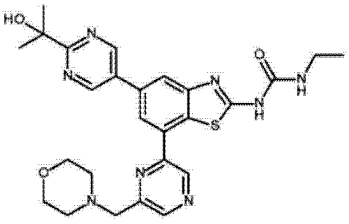
99；



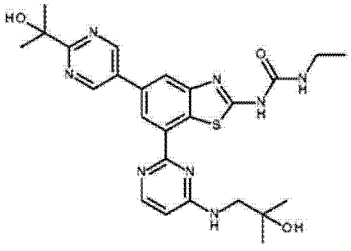
100；



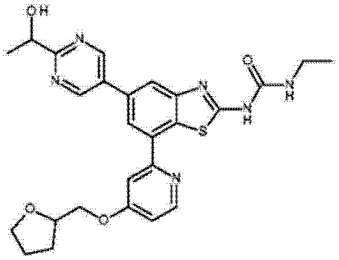
101；



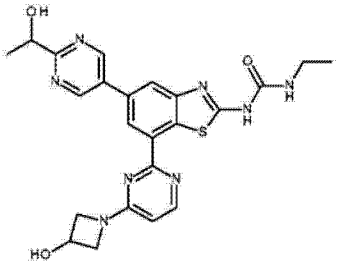
102；



103；

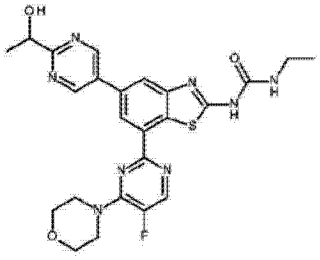


104；

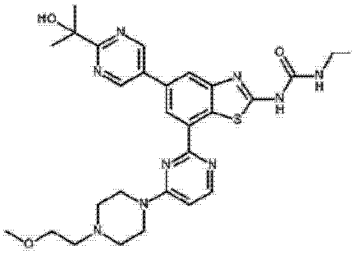


105；

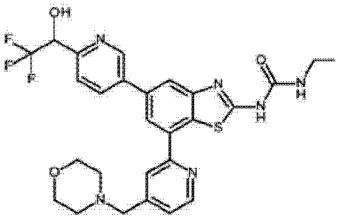
[0218]



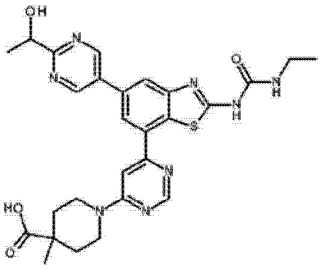
106；



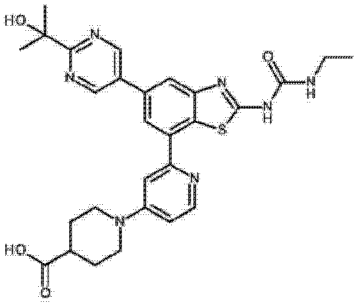
107；



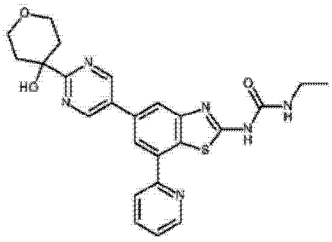
108；



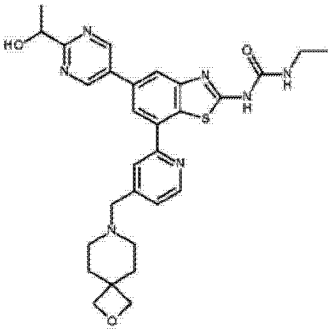
109；



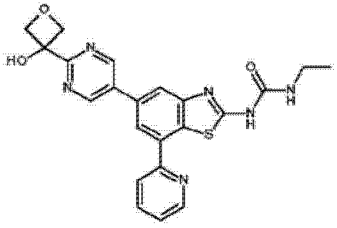
110；



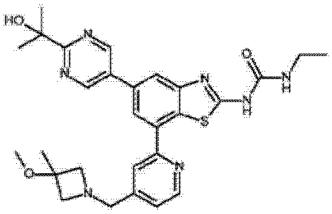
111；



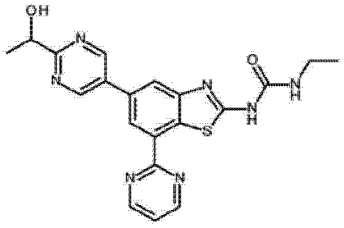
112；



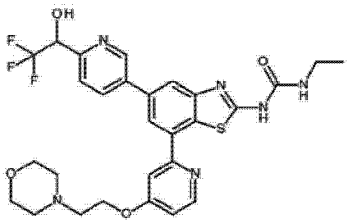
113；



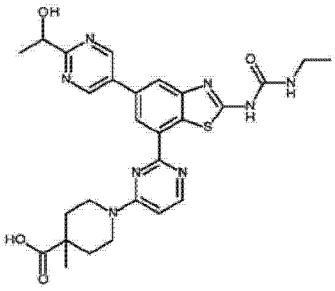
114；



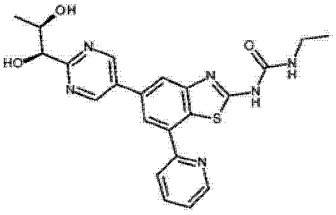
115；



116；

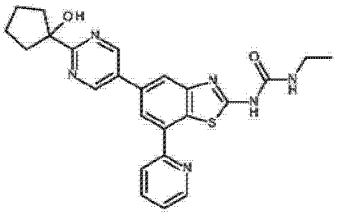


117；

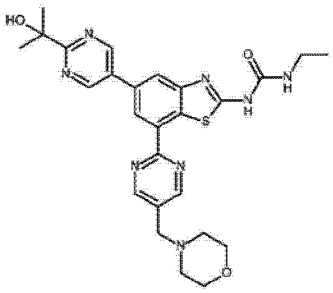


（混合物顺式二醇）

118；

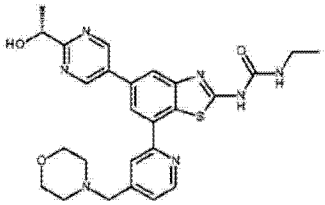


119；

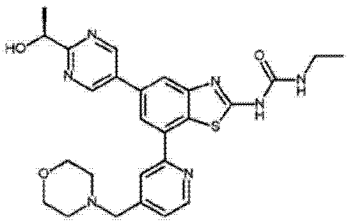


120；

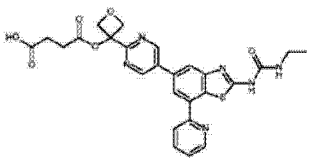
[0219]



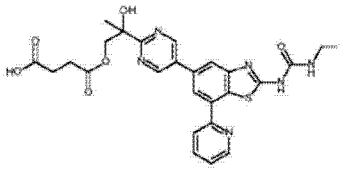
121；



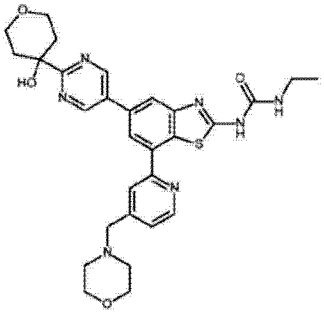
122；



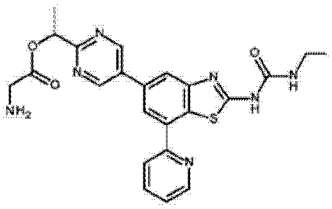
123；



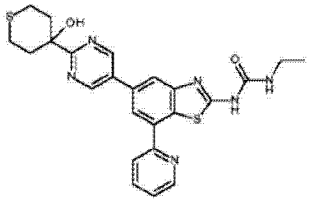
124；



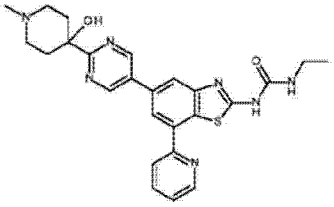
125；



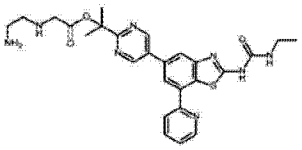
126；



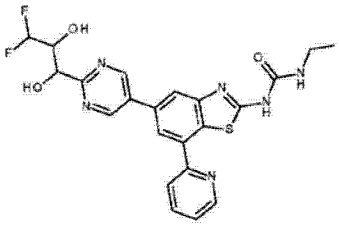
127；



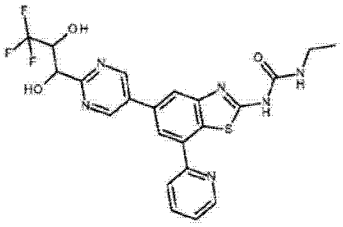
128；



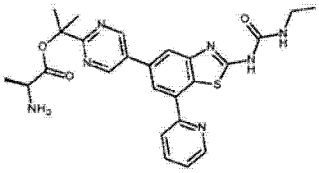
129；



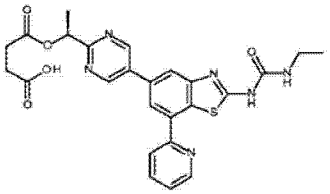
130；



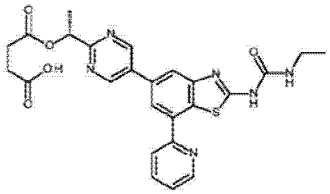
131；



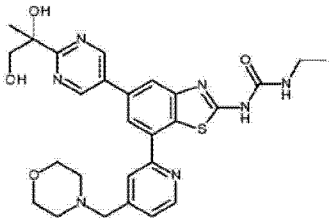
132；



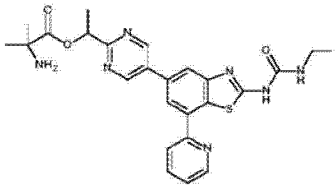
133；

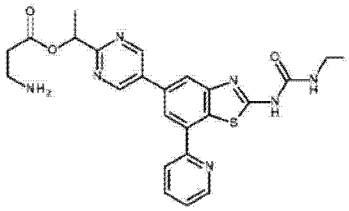


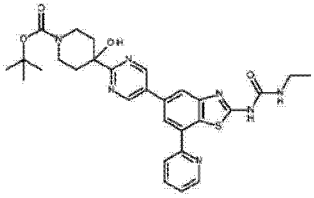
134；



135；



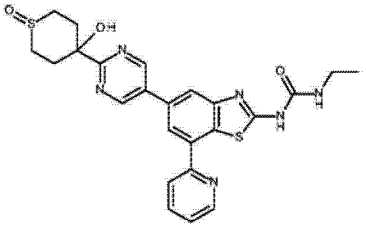




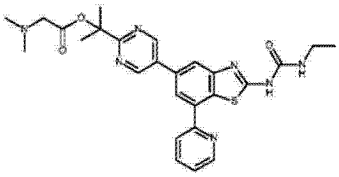
138；

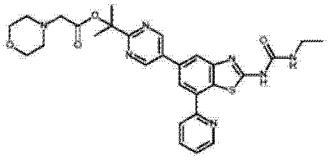
[0220]

136；



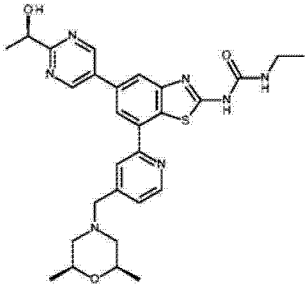
137；



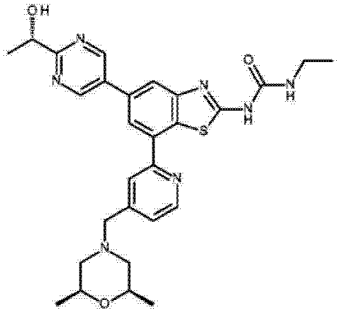


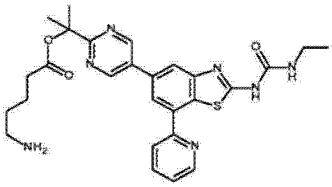
141；

139；



140；

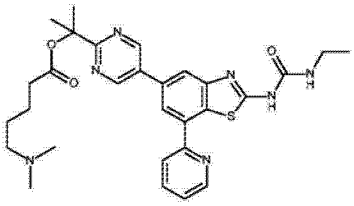


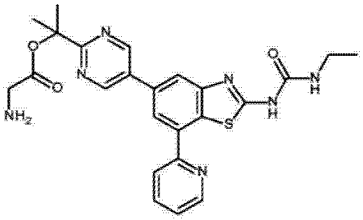


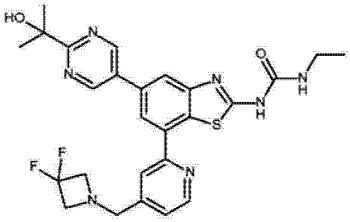
142；

143；

144；



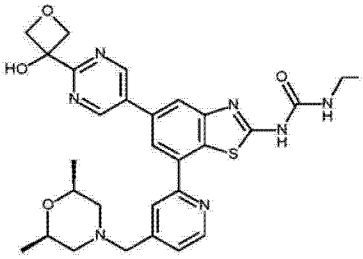


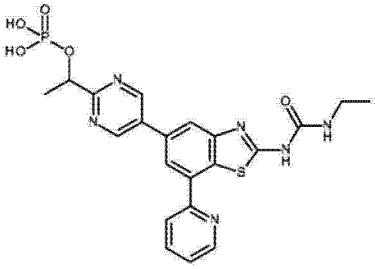


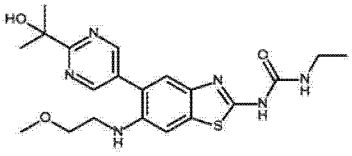
145；

146；

147；



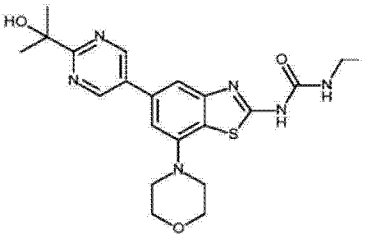


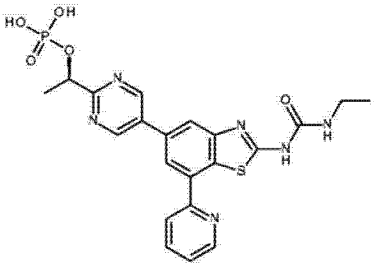


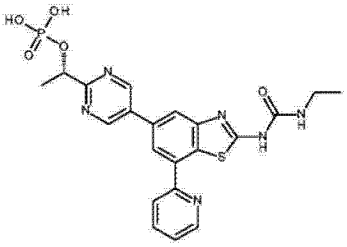
148；

149；

150；





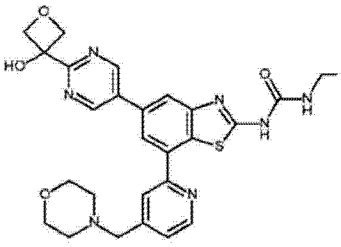


151；

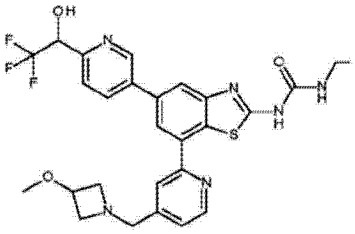
152；

153；

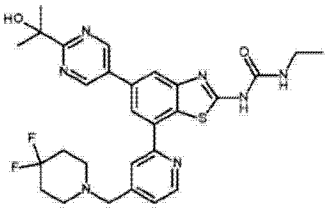
[0221]



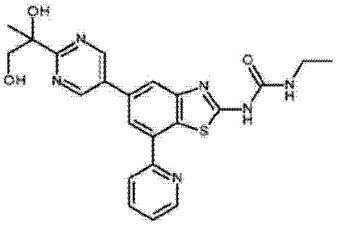
154；



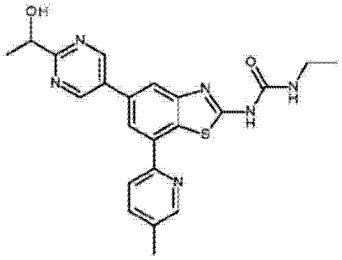
155；



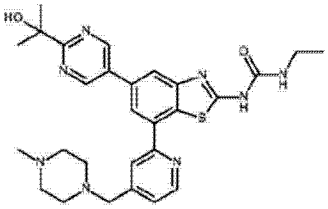
156；



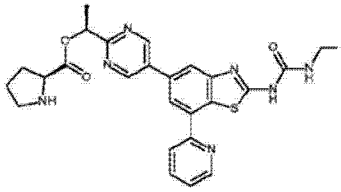
157；



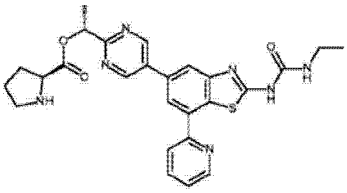
158；



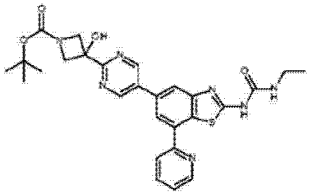
159；



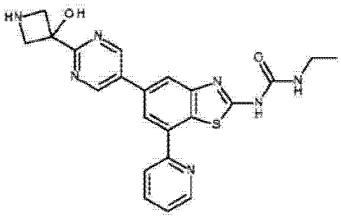
160；



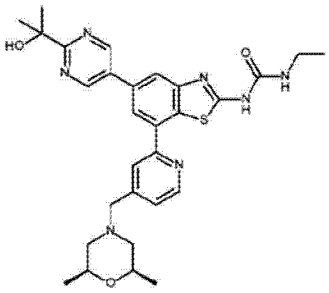
161；



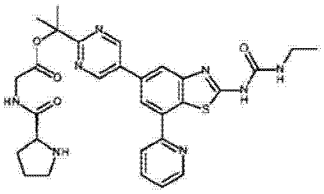
162；



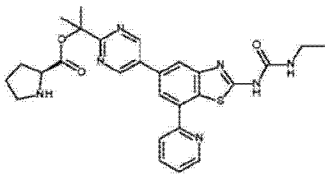
163；



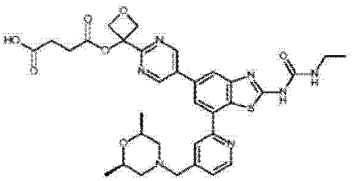
164；



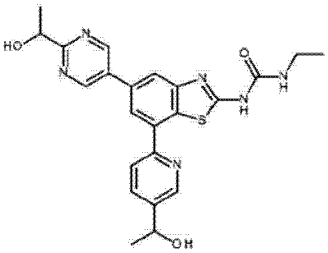
165；



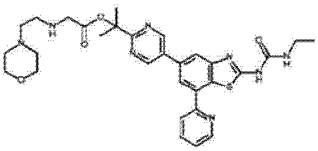
166；



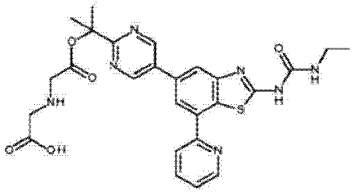
167；



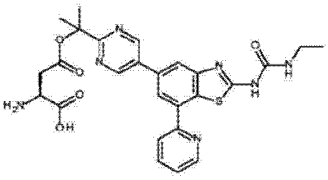
168；



169；

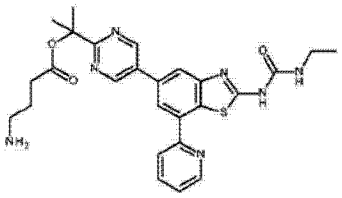


170；

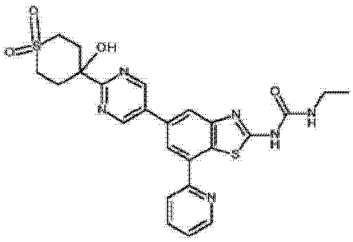


171；

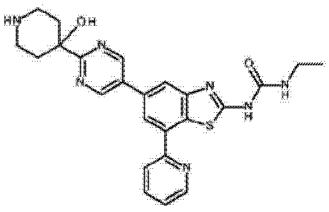
[0222]



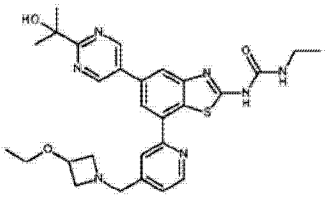
172；



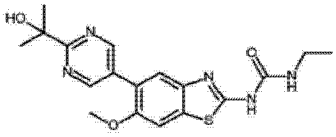
173；



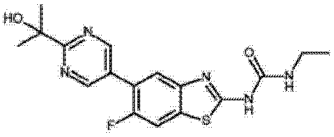
174；



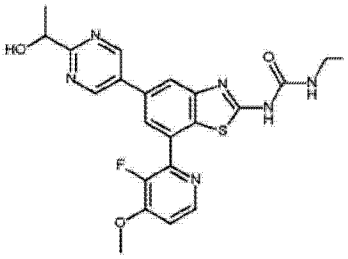
175；



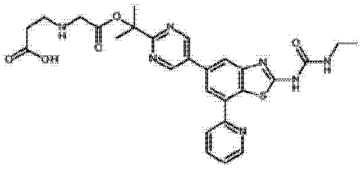
176；



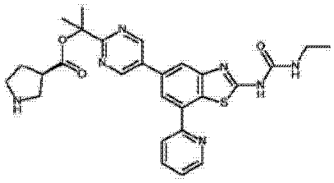
177；



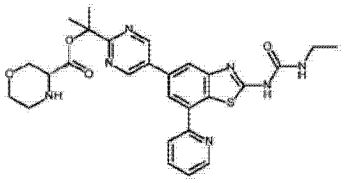
178；



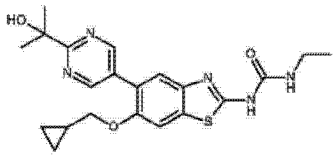
179；



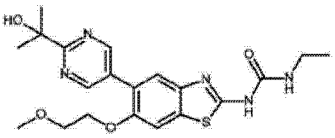
180；



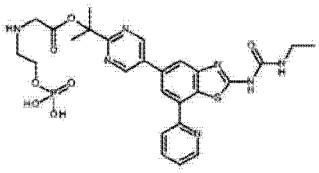
181；



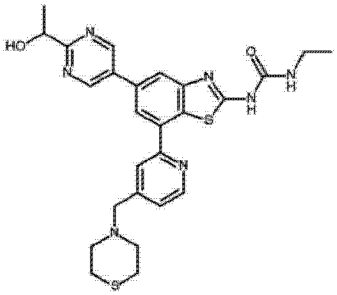
182；



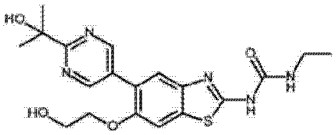
183；



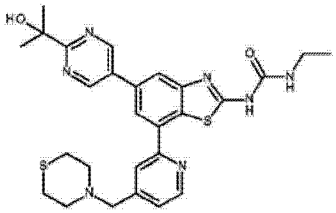
184；



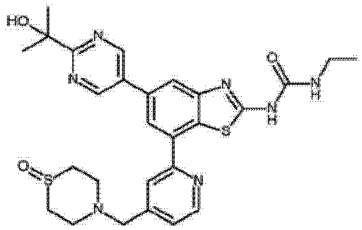
185；



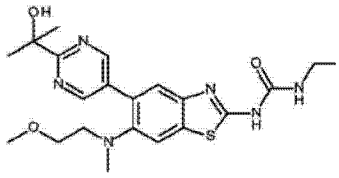
186；



187；

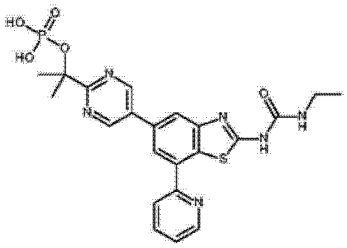


188；

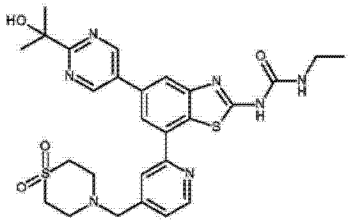


189；

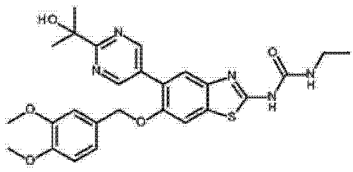
[0223]



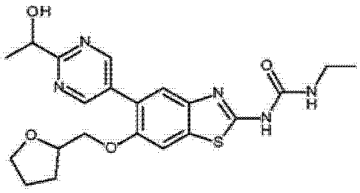
190；



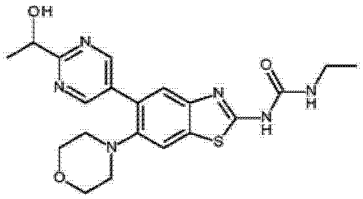
191；



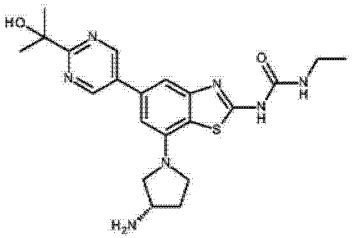
192；



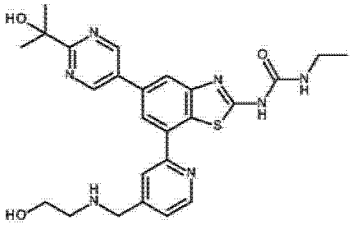
193；



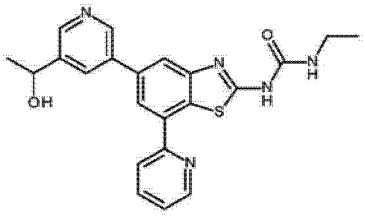
194；



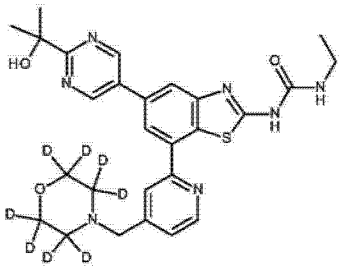
195；



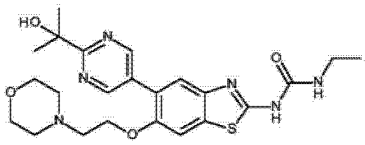
196；



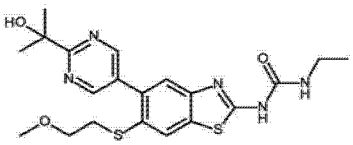
197；



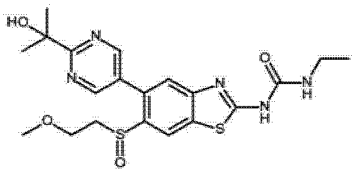
198；



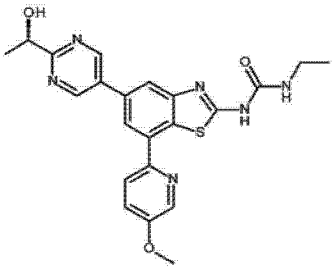
199；



200；



201；以及



202；

[0224] 其盐、外消旋体、非对映异构体、对映异构体、酯、氨基甲酸盐／酯、磷酸盐／酯、硫酸盐／酯、氘代形式和前药，其中化合物 1 至 202 的命名如下：

[0225] 1)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲；

[0226] 2)1- 乙基 -3-[7-[4-[(3- 羟基 -3- 甲基 - 氮杂环丁烷 -1- 基）甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲；

[0227] 3)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-6-(四氢呋喃 -2- 基

甲氧基)-1,3-苯并噻唑-2基]脲；

[0228] 4)1-乙基-3-[6-氟-5-[6-[羟基(3-吡啶基)甲基]-3-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0229] 5)1-(2-羟基乙基)-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0230] 6)1-乙基-3-[5-[5-(1-羟基乙基)吡嗪-2-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0231] 7)1-[5-[2-[(1S*,2R*)-1,2-二羟基丙基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲(混合物1-[5-[2-[(1S,2R)-1,2-二羟基丙基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲；和1-[5-[2-[(1R,2S)-1,2-二羟基丙基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲)；

[0232] 8)1-[5-[2-[(3R*,4S*)-3,4-二羟基四氢吡喃-4-基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲(混合物1-[5-[2-[(3R,4S)-3,4-二羟基四氢吡喃-4-基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲；以及1-[5-[2-[(3S,4R)-3,4-二羟基四氢吡喃-4-基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲)；

[0233] 9)1-乙基-3-[5-[4-(1-羟基乙基)三唑-1-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0234] 10)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-嘧啶-2-基-1,3-苯并噻唑-2基]脲；

[0235] 11)1-乙基-3-[5-[4-(1-羟基-1-甲基-乙基)咪唑-1-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0236] 12)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-甲氧基-1,3-苯并噻唑-2-基]脲；

[0237] 13)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-(甲氧基甲基)-1,3-苯并噻唑-2-基]脲；

[0238] 14)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[(6-甲基-3-吡啶基)甲氧基]-1,3-苯并噻唑-2-基]脲；

[0239] 15)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(甲基硫烷基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0240] 16)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(甲基亚磺酰基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0241] 17)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0242] 18)1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基4-甲基哌嗪-1-羧酸酯；

[0243] 19)4-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙氧基]-4-氧代-丁酸；

[0244] 20)04-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]01-甲基丁二酸酯；

[0245] 21)4-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙氧基]-4-氧代-丁酸；

[0246] 22)1-乙基-3-[5-[2-[(1R)-1-羟基乙基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0247] 23)1-乙基-3-[5-[2-[(1S)-1-羟基乙基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0248] 24)1-乙基-3-[5-[6-[羟基-(1-甲基咪唑-2-基)甲基]-3-吡啶基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0249] 25)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[5-(吗啉基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0250] 26)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(吡咯烷-1-基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0251] 27)1-乙基-3-[5-[6-(1-羟基-1-甲基-乙基)-3-吡啶基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0252] 28)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(吗啉基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0253] 29)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[(3-羟基吡咯烷-1-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0254] 30)1-乙基-3-[7-[4-[(3-羟基氮杂环丁烷-1-基)甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0255] 31)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[(3-甲氧基氮杂环丁烷-1-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0256] 32)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(2-吗啉基乙氧基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0257] 33)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(1-吗啉基乙基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0258] 34)1-[7-[4-[(3,3-二氟吡咯烷-1-基)甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

[0259] 35)1-乙基-3-[7-[4-[[(3S)-3-氟吡咯烷-1-基]甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0260] 36)1-乙基-3-[7-[4-[[(3R)-3-氟吡咯烷-1-基]甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0261] 37)1-[7-[4-[(3,3-二氟-1-哌啶基)甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

[0262] 38)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(3-吗啉基丙氧基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0263] 39)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-吡

嗪 -2- 基 -1,3- 苯并噻唑 -2 基] 脲 ;

[0264] 40)1-[5-[2-(1,2- 二羟基乙基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

[0265] 41)1-[7-(二甲基氨基甲基)-6- 羟基 -5-[6-(1- 羟基 -1- 甲基 - 乙基)-3- 吡啶基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

[0266] 42)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-[[(3R)-3- 甲氧基吡咯烷 -1- 基] 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

[0267] 43)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-(6- 甲基嘧啶 -4- 基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0268] 44)1- 乙基 -3-[6- 羟基 -5-[6-(1- 羟基 -1- 甲基 - 乙基)-3- 吡啶基]-7-(吗啉基甲基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0269] 45)1-[6-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-3- 吡啶基]-4- 甲基 - 哌啶 -4- 羧酸 ;

[0270] 46)2-[6-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-3- 吡啶基] 乙酸 ;

[0271] 47)1- 乙基 -3-[5-[2-(1- 羟基环己基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0272] 48)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 噻唑 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0273] 49)1- 乙基 -3-[5-[5-(1- 羟基 -1- 甲基 - 乙基) 吡嗪 -2- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0274] 50)1-[2-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-4- 吡啶基]-4- 甲基 - 哌啶 -4- 羧酸 ;

[0275] 51)1-[6-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-2- 吡啶基]-4- 甲基 - 哌啶 -4- 羧酸 ;

[0276] 52)1-[4-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基] 嘧啶 -2- 基]-4- 甲基 - 哌啶 -4- 羧酸 ;

[0277] 53)1-[7-[4-[(环丙基氨基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

[0278] 54)4-[[2-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基]-4- 吡啶基] 氨基]-1- 甲基 - 环己烷羧酸 ;

[0279] 55)1- 乙基 -3-[5-[2-(1- 羟基乙基) 嘧啶 -5- 基]-7-[4-(吗啉基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

[0280] 56)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[5-(2- 吗啉基乙氧基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

[0281] 57)1-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 丙基 - 脲 ;

[0282] 58)1-[5-[2-[环丙基 (羟基) 甲基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

[0283] 59)1-乙基-3-[5-[2-(1-羟基丙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0284] 60)1-乙基-3-[5-[2-(1-羟基-2,2-二甲基-丙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0285] 61)1-乙基-3-[5-[2-(1-羟基丁基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0286] 62)[(1R)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基](2R)-2-氨基-3-甲基-丁酸酯；

[0287] 63)[(1S)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基](2R)-2-氨基-3-甲基-丁酸酯；

[0288] 64)1-乙基-3-[7-[4-[[(3S)-3-氟吡咯烷-1-基]甲基]-2-吡啶基]-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0289] 65)1-乙基-3-[7-[4-[(3-羟基氮杂环丁烷-1-基)甲基]-2-吡啶基]-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0290] 66)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-[(3-羟基-3-甲基-氮杂环丁烷-1-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0291] 67)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[(3-羟基-3-甲基-吡咯烷-1-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0292] 68)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-[(3-甲基吗啉-4-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0293] 69)1-[7-[4-[[(2R,6S)-2,6-二甲基吗啉-4-基]甲基]-2-吡啶基]-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

[0294] 70)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-[(2,2,3,3,5,5,6,6-八氘代吗啉-4-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0295] 71)1-[7-[4-[(2,5-二甲基吗啉-4-基)甲基]-2-吡啶基]-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

[0296] 72)(2S)-1-[[2-[2-(乙基氨甲酰基氨基)-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-7-基]-4-吡啶基]甲基]吡咯烷-2-羧酸；

[0297] 73)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(6-氧杂-2-氮杂螺[3.3]庚烷-2-基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0298] 74)1-[5-[2-(乙基氨甲酰基氨基)-7-[4-(1-羟基-1-甲基-乙基)-2-吡啶基]-1,3-苯并噻唑-5-基]嘧啶-2-基]-4-甲基-哌啶-4-羧酸；

[0299] 75)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(2-吗啉基乙氧基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0300] 76)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-[(3-甲氧基氮杂环丁烷-1-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0301] 77)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-[[(3R)-3-羟基吡咯烷-1-基]甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0302] 78)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(2-甲氧基

乙基氨基）嘧啶 -2- 基]-1,3- 苯并噻唑 -2- 基] 脲；

[0303] 79)1- 乙基 -3-[7-[4-(4- 乙基哌嗪 -1- 基）嘧啶 -2- 基]-5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲；

[0304] 80)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-7-[4-(2- 甲氧基乙氧基）-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲；

[0305] 81)1- 乙基 -3-[5-[2-(1- 羟基 -2- 吗啉基 - 乙基）嘧啶 -5- 基]-7-(2- 吡啶基）-1,3- 苯并噻唑 -2- 基] 脲；

[0306] 82)1-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-7-(2- 吡啶基）-1,3- 苯并噻唑 -2- 基]-3- 甲基 - 脲；

[0307] 83)1-[5-[2-(1- 羟基乙基）嘧啶 -5- 基]-7-(2- 吡啶基）-1,3- 苯并噻唑 -2- 基]-3- 甲基 - 脲；

[0308] 84)1- 乙基 -3-[5-[2-(1- 羟基乙基）嘧啶 -5- 基]-7-[4-[(3- 羟基 -3- 甲基 - 吡咯烷 -1- 基）甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲；

[0309] 85)1- 乙基 -3-[7-[4-(2- 羟基乙基氨基）嘧啶 -2- 基]-5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲；

[0310] 86)1- 乙基 -3-[7-[4-(3- 羟基 -3- 甲基 - 氮杂环丁烷 -1- 基）嘧啶 -2- 基]-5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲；

[0311] 87)1-[6-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基] 嘧啶 -4- 基]-4- 甲基 - 哌啶 -4- 羧酸；

[0312] 88)1-[5-[2-(乙基氨甲酰基氨基)-7-[4-(1- 羟基乙基）-2- 吡啶基]-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-4- 甲基 - 哌啶 -4- 羧酸；

[0313] 89)[1-[5-[2-(乙基氨基甲酰基氨基)-7-(2- 吡啶基）-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙基]4- 甲基哌嗪 -1- 羧酸酯；

[0314] 90)1- 乙基 -3-[5-[2-(1- 羟基乙基）嘧啶 -5- 基]-7-(4- 羟基 -2- 吡啶基）-1,3- 苯并噻唑 -2- 基] 脲；

[0315] 91)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-7-[4-(2- 吗啉基乙基氨基）嘧啶 -2- 基]-1,3- 苯并噻唑 -2- 基] 脲；

[0316] 92)1- 乙基 -3-[5-[2-(1- 羟基乙基）嘧啶 -5- 基]-7-[4-(2- 甲氧基乙氧基）-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲；

[0317] 93)1- 乙基 -3-[5-[2-(1- 羟基乙基）嘧啶 -5- 基]-7-[4-[(3- 甲氧基氮杂环丁烷 -1- 基）嘧啶 -2- 基]-1,3- 苯并噻唑 -2- 基] 脲；

[0318] 94)1- 乙基 -3-[5-[2-(1- 羟基乙基）嘧啶 -5- 基]-7-(4- 吗啉基嘧啶 -2- 基）-1,3- 苯并噻唑 -2- 基] 脲；

[0319] 95)1- 乙基 -3-[5-[6-(1- 羟基乙基）-3- 吡啶基]-7-(2- 吡啶基）-1,3- 苯并噻唑 -2- 基] 脲；

[0320] 96)1- 乙基 -3-[7-(2- 吡啶基）-5-[6-(2,2,2- 三氟 -1- 羟基 - 乙基）-3- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲；

[0321] 97)1-[2-[2-(乙基氨甲酰基氨基)-5-[2-(1- 羟基 -1- 甲基 - 乙基）嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基] 嘧啶 -4- 基]-4- 甲基 - 哌啶 -4- 羧酸；

[0322] 98)1-乙基-3-[5-[2-(1-乙基-1-羟基-丙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0323] 99)1-[5-[2-(乙基氨甲酰基氨基)-7-[5-(1-羟基-1-甲基-乙基)-2-吡啶基]-1,3-苯并噻唑-5-基]嘧啶-2-基]-4-甲基-哌啶-4-羧酸；

[0324] 100)1-[7-[4-(二乙氧基磷酰基甲基)-2-吡啶基]-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

[0325] 101)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(吗啉基甲基)嘧啶-2-基]-1,3-苯并噻唑-2-基]脲；

[0326] 102)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[6-(吗啉基甲基)吡嗪-2-基]-1,3-苯并噻唑-2-基]脲；

[0327] 103)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[(2-羟基-2-甲基-丙基)氨基]嘧啶-2-基]-1,3-苯并噻唑-2-基]脲；

[0328] 104)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(四氢呋喃-2-基甲氧基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0329] 105)1-乙基-3-[7-[4-(3-羟基氮杂环丁烷-1-基)嘧啶-2-基]-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0330] 106)1-乙基-3-[7-(5-氟-4-吗啉基-嘧啶-2-基)-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0331] 107)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[4-(2-甲氧基乙基)哌嗪-1-基]嘧啶-2-基]-1,3-苯并噻唑-2-基]脲；

[0332] 108)1-乙基-3-[7-[4-(吗啉基甲基)-2-吡啶基]-5-[6-(2,2,2-三氟-1-羟基-乙基)-3-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0333] 109)1-[6-[2-(乙基氨甲酰基氨基)-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-7-基]嘧啶-4-基]-4-甲基-哌啶-4-羧酸；

[0334] 110)1-[2-[2-(乙基氨甲酰基氨基)-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-7-基]-4-吡啶基]哌啶-4-羧酸；

[0335] 111)1-乙基-3-[5-[2-(4-羟基四氢吡喃-4-基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0336] 112)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(2-氧杂-7-氮杂螺[3.5]壬烷-7-基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0337] 113)1-乙基-3-[5-[2-(3-羟基氧杂环丁烷-3-基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0338] 114)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[(3-甲氧基-3-甲基-氮杂环丁烷-1-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0339] 115)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-嘧啶-2-基-1,3-苯并噻唑-2-基]脲；

[0340] 116)1-乙基-3-[7-[4-(2-吗啉基乙氧基)-2-吡啶基]-5-[6-(2,2,2-三氟-1-羟基-乙基)-3-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0341] 117)1-[2-[2-(乙基氨甲酰基氨基)-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯

并噻唑 -7- 基] 嘧啶 -4- 基]-4- 甲基 - 哌啶 -4- 羧酸 ;

[0342] 118)1-[5-[2-[(1R*,2R*)-1,2- 二 羟 基 丙 基] 嘧 啶 -5- 基]-7-(2- 吡 啶 基)-1,3- 苯 并 噻 唑 -2- 基]-3- 乙 基 - 脲 (混 合 物 1-[5-[2-[(1R,2R)-1,2- 二 羟 基 丙 基] 嘧 啶 -5- 基]-7-(2- 吡 啶 基)-1,3- 苯 并 噻 唑 -2- 基]-3- 乙 基 - 脲 ; 和 1-[5-[2-[(1S,2S)-1,2- 二 羟 基 丙 基] 嘧 啶 -5- 基]-7-(2- 吡 啶 基)-1,3- 苯 并 噻 唑 -2- 基]-3- 乙基 - 脲) ;

[0343] 119)1- 乙基 -3-[5-[2-(1- 羟基环戊基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0344] 120)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[5-(吗啉基甲基) 嘧啶 -2- 基]-1,3- 苯并噻唑 -2- 基] 脲 ;

[0345] 121)1- 乙 基 -3-[5-[2-[(1R)-1- 羟 基 乙 基] 嘧 啶 -5- 基]-7-[4-(吗 啉 基 甲 基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

[0346] 122)1- 乙 基 -3-[5-[2-[(1S)-1- 羟 基 乙 基] 嘧 啶 -5- 基]-7-[4-(吗 啉 基 甲 基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

[0347] 123)4-[3-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 氧杂环丁烷 -3- 基] 氧基 -4- 氧代 - 丁酸 ;

[0348] 124)4-[2-[5-[2-(乙基氨基甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-2- 羟基 - 丙氧基]-4- 氧代 - 丁酸 ;

[0349] 125)1- 乙基 -3-[5-[2-(4- 羟基四氢吡喃 -4- 基) 嘧啶 -5- 基]-7-[4-(吗啉基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

[0350] 126)1-[5-[2-(乙基氨基甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基 2- 氨基乙酸酯 ;

[0351] 127)1- 乙 基 -3-[5-[2-(4- 羟 基 四 氢 噻 喃 -4- 基) 嘧 啶 -5- 基]-7-(2- 吡 啶 基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0352] 128)1- 乙基 -3-[5-[2-(4- 羟基 -1- 甲基 -4- 哌啶基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0353] 129)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙基]2-(2- 氨基乙基氨基) 乙酸酯 ;

[0354] 130)1-[5-[2-[(1R*,2S*)-3,3- 二氟 -1,2- 二羟基 - 丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 (混合物 1-[5-[2-[(1R,2S)-3,3- 二氟 -1,2- 二羟基 - 丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ; 和 1-[5-[2-[(1S,2R)-3,3- 二氟 -1,2- 二羟基 - 丙基] 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲) ;

[0355] 131)1- 乙 基 -3-[7-(2- 吡 啶 基)-5-[2-[(1R*,2S*)-3,3,3- 三 氟 -1,2- 二 羟 基 - 丙基] 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲 (混合物 1- 乙基 -3-[7-(2- 吡啶基)-5-[2-[(1R,2S)-3,3,3- 三 氟 -1,2- 二 羟 基 - 丙 基] 嘧 啶 -5- 基]-1,3- 苯 并 噻 唑 -2- 基] 脲 ; 和 1- 乙基 -3-[7-(2- 吡啶基)-5-[2-[(1S,2R)-3,3,3- 三氟 -1,2- 二羟基 - 丙基] 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲) ;

[0356] 132)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧

啶 -2- 基]-1- 甲基 - 乙基](2S)-2- 氨基丙酸酯；

[0357] 133)4-[(1S)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙氧基]-4- 氧代 - 丁酸；

[0358] 134)4-[(1R)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙氧基]-4- 氧代 - 丁酸；

[0359] 135)1-[5-[2-(1,2- 二羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-(吗啉基甲基)-2- 吡啶基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲；

[0360] 136)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基 2- 氨基 -2- 甲基 - 丙酸酯；

[0361] 137)1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基 3- 氨基丙酸酯；

[0362] 138) 叔丁基 4-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-4- 羟基 - 哌啶 -1- 羧酸酯；

[0363] 139)1- 乙基 -3-[5-[2-(4- 羟基 -1- 氧代 - 硫杂环戊烷 -4- 基) 嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲；

[0364] 140)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙基]2-(二甲基氨基) 乙酸酯；

[0365] 141)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙基]2- 吗啉基乙酸酯；

[0366] 142)1-[7-[4-[[(2R,6S)-2,6- 二甲基吗啉 -4- 基] 甲基]-2- 吡啶基]-5-[2-[(1R)-1- 羟基乙基] 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲；

[0367] 143)1-[7-[4-[[(2R,6S)-2,6- 二甲基吗啉 -4- 基] 甲基]-2- 吡啶基]-5-[2-[(1S)-1- 羟基乙基] 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲；

[0368] 144)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙基]5- 氨基戊酸酯；

[0369] 145)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙基]5-(二甲基氨基) 戊酸酯；

[0370] 146)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-1- 甲基 - 乙基]2- 氨基乙酸酯；

[0371] 147)1-[7-[4-[(3,3- 二氟氮杂环丁烷 -1- 基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲；

[0372] 148)1-[7-[4-[[(2R,6S)-2,6- 二甲基吗啉 -4- 基] 甲基]-2- 吡啶基]-5-[2-(3- 羟基氧杂环丁烷 -3- 基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲；

[0373] 149)1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基磷酸二氢酯；

[0374] 150)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-6-(2- 甲氧基乙基氨基)-1,3- 苯并噻唑 -2- 基] 脲；

[0375] 151)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7- 吗啉基 -1,3- 苯并噻唑 -2- 基] 脲；

[0376] 152)[(1R)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基]磷酸二氢酯；

[0377] 153)[(1S)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基]磷酸二氢酯；

[0378] 154)1-乙基-3-[5-[2-(3-羟基氧杂环丁烷-3-基)嘧啶-5-基]-7-[4-(吗啉基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0379] 155)1-乙基-3-[7-[4-[(3-甲氧基氮杂环丁烷-1-基)甲基]-2-吡啶基]-5-[6-(2,2,2-三氟-1-羟基-乙基)-3-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0380] 156)1-[7-[4-[(4,4-二氟-1-哌啶基)甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

[0381] 157)1-[5-[2-(1,2-二羟基-1-甲基-乙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲；

[0382] 158)1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-(5-甲基-2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0383] 159)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[(4-甲基哌嗪-1-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0384] 160)[(1S)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基](2S)-吡咯烷-2-羧酸酯；

[0385] 161)[(1R)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基](2S)-吡咯烷-2-羧酸酯；

[0386] 162)叔丁基3-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-3-羟基-氮杂环丁烷-1-羧酸酯；

[0387] 163)1-乙基-3-[5-[2-(3-羟基氮杂环丁烷-3-基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0388] 164)1-[7-[4-[[(2R,6S)-2,6-二甲基吗啉-4-基]甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

[0389] 165)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]2-[[(2S)-吡咯烷-2-羰基]氨基]乙酸酯；

[0390] 166)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基](2S)-吡咯烷-2-羧酸酯；

[0391] 167)4-[3-[5-[7-[4-[[(2R,6S)-2,6-二甲基吗啉-4-基]甲基]-2-吡啶基]-2-(乙基氨甲酰基氨基)-1,3-苯并噻唑-5-基]嘧啶-2-基]氧杂环丁烷-3-基]氧基-4-氧代-丁酸；

[0392] 168)1-乙基-3-[7-[5-(羟基乙基)-2-吡啶基]-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0393] 169)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]2-(2-吗啉基乙基氨基)乙酸酯；

[0394] 170)2-[[2-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙氧基]-2-氧代-乙基]氨基]乙酸；

[0395] 171)(2S)-2-氨基-4-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙氧基]-4-氧代-丁酸；

[0396] 172)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]4-氨基丁酸酯；

[0397] 173)1-乙基-3-[5-[2-(4-羟基-1,1-二氧代-硫杂环戊烷-4-基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0398] 174)1-乙基-3-[5-[2-(4-羟基-4-哌啶基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲；

[0399] 175)1-[7-[4-[(3-乙氧基氮杂环丁烷-1-基)甲基]-2-吡啶基]-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

[0400] 176)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-6-甲氧基-1,3-苯并噻唑-2-基]脲；

[0401] 177)1-乙基-3-[6-氟-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0402] 178)1-乙基-3-[7-(3-氟-4-甲氧基-2-吡啶基)-5-[2-[1-羟基乙基]嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0403] 179)3-[[2-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙氧基]-2-氧代-乙基]氨基]丙酸；

[0404] 180)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基](3R)-吡咯烷-3-羧酸酯；

[0405] 181)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基](3R)-吗啉基-3-羧酸酯；

[0406] 182)1-[6-(环丙基甲氧基)-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲；

[0407] 183)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-6-(2-甲氧基乙氧基)-1,3-苯并噻唑-2-基]脲；

[0408] 184)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]2-(2-膦酰氧基乙基氨基)乙酸酯；

[0409] 185)1-乙基-3-[5-[2-[1-羟基乙基]嘧啶-5-基]-7-[4-(硫代吗啉基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0410] 186)1-乙基-3-[6-(2-羟基乙氧基)-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]脲；

[0411] 187)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-(硫代吗啉基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0412] 188)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-[4-[(1-氧代-1,4-噻嗪-4-基)甲基]-2-吡啶基]-1,3-苯并噻唑-2-基]脲；

[0413] 189)1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-6-[2-甲氧基乙基(甲基)氨基]-1,3-苯并噻唑-2-基]脲；

[0414] 190)[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧

啶 -2- 基]-1- 甲基 - 乙基] 磷酸二氢酯 ;

[0415] 191)1-[7-[4-[(1,1- 二氧代 -1,4- 噻嗪 -4- 基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

[0416] 192)1-[6-[(3,4- 二甲氧基苯基) 甲氧基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

[0417] 193)1- 乙基 -3-[5-[2-[1- 羟基乙基] 嘧啶 -5- 基]-6-(四氢呋喃 -2- 基甲氧基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0418] 194)1- 乙基 -3-[5-[2-[1- 羟基乙基] 嘧啶 -5- 基]-6- 吗啉基 -1,3- 苯并噻唑 -2- 基] 脲 ;

[0419] 195)1-[7-[(3S)-3- 氨基吡咯烷 -1- 基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 ;

[0420] 196)1- 乙基 -3-[7-[4-[(2- 羟基乙基氨基) 甲基]-2- 吡啶基]-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基] 脲 ;

[0421] 197)1- 乙基 -3-[5-[5-(1- 羟基乙基)-3- 吡啶基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0422] 198)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-7-[4-[(2,2,3,3,5,5,6,6- 八氘代吗啉 -4- 基) 甲基]-2- 吡啶基]-1,3- 苯并噻唑 -2- 基] 脲 ;

[0423] 199)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-6-(2- 吗啉基乙氧基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0424] 200)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-6-(2- 甲氧基乙基硫烷基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0425] 201)1- 乙基 -3-[5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-6-(2- 甲氧基乙基亚磺酰基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0426] 202)1- 乙基 -3-[5-[2-[(1R)-1- 羟基乙基] 嘧啶 -5- 基]-7-(5- 甲氧基 -2- 吡啶基)-1,3- 苯并噻唑 -2- 基] 脲 ;

[0427] 在另一个特定实施方式中,优选这些化合物的酯 (优选酯前药) 及其盐、外消旋体、非对映异构体、对映异构体和氘代形式。在另一个特定实施方式中,优选这些化合物的磷酸盐 / 酯 (优选磷酸盐 / 酯前药) 及其盐、外消旋体、非对映异构体、对映异构体和氘代形式。

[0428] 因此,在一个实施方式中,所述化合物选自以下化合物中任意一个的酯或磷酸盐 / 酯 :化合物 18、19、20、21、62、63、123、126、129、132、133、134、136、137、140、141、144、145、146、149、152、153、160、161、165、166、167、169、170、171、172、179、180、181、184 和 190、其盐、外消旋体、非对映异构体、对映异构体和氘代形式。

[0429] 式 (I) 的化合物的盐优选是药学上可接受的,但应理解非药学上可接受的盐也在本发明范围内,因为其可用作制备药学上可接受的盐的中间体。

[0430] 合适的药学上可接受的盐包括但不限于药学上可接受的无机酸 (如盐酸、硫酸、磷酸、硝酸、碳酸、硼酸、氨基磺酸和氢溴酸) 的盐,或药学上可接受的有机酸 (如乙酸、丙酸、丁酸、酒石酸、马来酸、羟基马来酸、反丁烯二酸、马来酸、丙二酸、羟基马来酸、富马酸、

苹果酸、柠檬酸、乳酸、粘酸、葡糖酸、苯甲酸、琥珀酸、草酸、苯基乙酸、甲磺酸、甲苯磺酸、苯磺酸、乙烷 -1,2- 二磺酸、水杨酸、对氨基苯磺酸、天冬氨酸、谷氨酸、龙胆酸、依地酸、硬脂酸、棕榈酸、双羟萘酸、油酸、月桂酸、泛酸、鞣酸、抗坏血酸和戊酸）的盐。

[0431] 碱性盐包括但不限于由药学上可接受的阳离子形成的那些，如钠盐、钾盐、锂盐、钙盐、镁盐、锌盐、铵盐、烷基铵盐（如由三乙胺形成的盐）、烷氧基铵盐（如由乙醇胺形成的那些）以及由乙二胺、胆碱或者氨基酸（如精氨酸、赖氨酸或组氨酸）形成的盐。药学上可接受的盐的类型及其形成的一般信息是本领域技术人员已知的，并且描述于通用教材如“Handbook of Pharmaceutical salts(《药用盐手册》)”P.H.Stahl、C.G.Wermuth，第 1 版，2002，威利 - 德国化学学会出版社 (Wiley-VCH)。

[0432] 可以使用特定试剂对碱性含氮基团进行季铵化，所述试剂是例如低级烷基卤化物（如甲烷、乙烷、丙烷和丁烷的氯化物、溴化物和碘化物）；硫酸二烷基酯（如硫酸二甲酯和硫酸二乙酯）；和其他基团（如烷基膦酸酯或氨基磷酸酯）。

[0433] 羟基基团可以用包括低级烷基羧酸（如乙酸和 2,2- 二甲基丙酸）的基团来酯化，或用包括烷基磺酸（如甲磺酸）的基团来磺酸化，或用包括烷基膦酸（如亚甲基膦酸）的基团来磷酸化，或直接连接至膦酸酯、次膦酸酯或磷酸酯。

[0434] 应认识到式 I 化合物可以具有不对称中心，因此能以一种以上的立体异构体形式存在。本发明还涉及一个或多个不对称中心的基本纯异构体形式的化合物，如约大于 90% ee，如约 95% 或 97% ee，或大于 99% ee，及其混合物，包括外消旋混合物。这些异构体可以采用不对称合成（例如用手性中间体）或通过手性拆分来制备。

[0435] 本发明还包括式 (I) 的化合物的前药。有游离氨基、酰氨基、羟基或羧基的式 (I) 的化合物能转化成前药。

[0436] 特别优选的是带有羟基基团的前药（如氨基甲酸盐 / 酯、磷酸盐 / 酯、硫酸盐 / 酯和酯），包括来源于氨基酸和二肽的那些和设计用来通过前药部分的水解或内部环化以释放母体的部分。

[0437] 组合物

[0438] 还提供了一种组合物，所述组合物包括式 (I) 的化合物、其盐、异构体、外消旋体、非对映异构体、对映异构体和前药。

[0439] 优选地，所述组合物还包含药学上可接受的载剂、稀释剂或赋形剂。

[0440] 可例如通过使用常规固体或液体载剂或稀释剂以及适于所需给药模式类型的药学添加剂（例如赋形剂、粘结剂、防腐剂、稳定剂、风味剂等）按照药学制剂领域熟知的技术来配制本发明组合物。

[0441] 药物制剂包括适于口服、直肠、经鼻、局部（包括口颊和舌下）、阴道或肠胃外（包括肌肉内、皮下和静脉内）给予的那些或以适于吸入或吹入给予的形式。可以药物组合物及其单位剂量的形式将本发明的化合物与传统的佐剂、载剂或稀释剂一起配置，并且所述形式可以是固体（如药片或填充的胶囊）或液体（如溶液、悬浮液、乳液、酏剂或相同填充的胶囊），全部用于口服，以栓剂形式用于直肠给予；或以无菌注射溶液形式用于胃肠外（包含皮下）使用。

[0442] 在一个实施方式中，本发明的组合物可配置用于口服给药和 / 或静脉内 (IV) 给药。

[0443] 在另一个实施方式中，本发明组合物可与另一种抗菌剂联合给药或额外包括另一种抗菌剂。合适的抗菌剂是本领域技术人员熟悉的，包括青霉素、头孢菌素、碳青霉烯、单环β－内酰胺、β－内酰胺、糖肽、氨基糖苷、四环素、大环内酯、酮内酯、喹诺酮、氟喹诺酮、噁唑烷酮、香豆素、环噻啶、万古霉素及其衍生物。

[0444] 治疗方法

[0445] 本发明提供了治疗细菌感染的方法，所述方法包括向患有所述感染的对象给予式(I)化合物或其药学上可接受的盐。

[0446] 本发明的化合物可以通过任何合适方法给药，例如，口服、胃肠外（如通过皮下、静脉内、肌肉内、或脑池内注射）或输注技术（例如，作为无菌可注射水性或非水性溶液或悬浮液）。

[0447] 本发明还提供了式(I)的化合物或其药学上可接受的盐用于治疗细菌感染。

[0448] 术语“有效量”指引发研究人员、兽医、医生或其它临床工作人员所寻求组织、体系、动物或人的生物学或医学反应的对象组合物用量。

[0449] 本文所用术语“组合物”旨在包括含有特定量特定成分的产品，以及从特定量的特定成分组合直接或间接生成的任何产品。“药学上可接受的”指载剂、稀释剂或者赋形剂必须与制剂中其它成分相容，且对接受者没有毒害作用。

[0450] 术语“给药”和／或“给予”化合物应理解为向需要治疗的个体提供本发明的化合物。

[0451] 用于给予本发明化合物的药物组合物可方便地以剂量单位的形式呈现，并可由制药领域熟知的任何方法制备。所有方法均包括使活性成分与构成一种或多种附加成分的载剂结合的步骤。通常，使活性成分与液体载剂和／或细分固体载剂均一且密切地结合以制备药物组合物，然后，如果需要，将该产物成型至所需制剂。在药物组合物中，活性对象化合物的含量足以对疾病的过程或病症产生所需的影响。本文所用术语“组合物”旨在包括含有特定量特定成分的产品，以及直接或间接来自特定量的特定成分组合的产品。

[0452] 药物组合物可以是无菌可注射水性或油性悬浮液的形式。可按照本领域已知方法，用如上所述合适的分散剂或湿润剂和助悬剂配制该悬浮液。无菌注射剂也可以是胃肠道外可接受的无毒稀释剂或溶剂配制的无菌注射溶液或悬浮液，例如在1,3-丁二醇中配制的溶液。可用的可接受载剂和溶剂是水、林格氏溶液和等渗氯化钠溶液。此外，通常采用无菌非挥发油作为溶剂或悬浮介质。出于此种目的，可采用任何刺激性小的非挥发油，包括合成的甘油单酯或甘油二酯。此外，脂肪酸（如油酸）可用于制备注射剂。

[0453] 在治疗或预防细菌感染中，合适的剂量水平通常是约0.01-500mg/kg患者体重／天，能以单个或多个剂量给药。对于口服给药，优选以片剂形式提供该组合物，其中含有1.0-1000毫克活性成分。

[0454] 然而，应理解任何具体患者的特定剂量水平和剂量频率可能不同，这取决于各种因素，包括所用特定化合物的活性、该化合物的代谢稳定性和作用长度、年龄、体重、总体健康状况、性别、饮食，给药方式和时间、排泄率、联合用药、具体病症的严重程度和接受治疗的宿主。

[0455] 除了灵长类动物如人以外，可以根据本发明方法治疗各种其他哺乳动物。例如，能治疗哺乳动物，包括但不限于母牛、绵羊、山羊、马、狗、猫、豚鼠、大鼠或其他牛、绵羊、山羊、

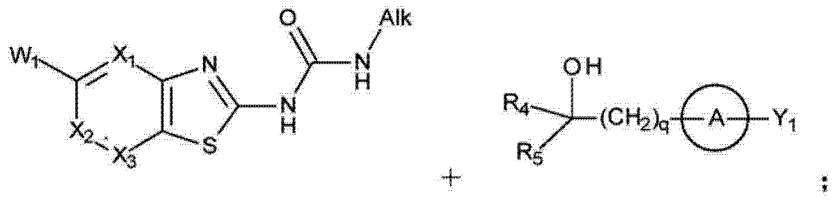
马、犬、猫、啮齿动物或鼠种。然而，所述方法也能应用于其他物种，例如禽鸟物种（如鸡）。

[0456] 上述方法治疗的对象是哺乳动物，包括但不限于母牛、绵羊、山羊、马、狗、猫、豚鼠、大鼠或其他牛、绵羊、山羊、马、犬、猫、啮齿动物或鼠种，并且优选人类，男性或女性。

[0457] 制备方法

[0458] 通常，本发明的组合物可通过在所述条件下将式(i-a)的中间物与式(ii-a)的前体偶联来制备：

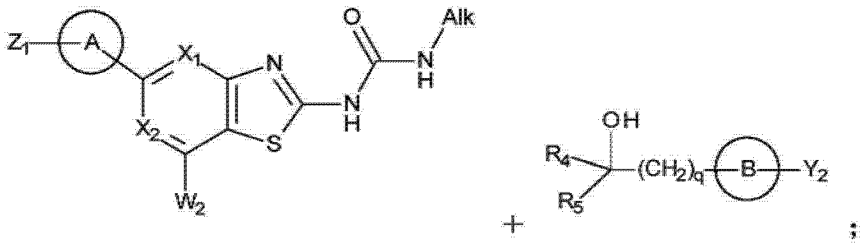
[0459]



(i-a) (ii-a)

[0460] 或者将式(i-b)的中间体与式(ii-b)的前体偶联：

[0461]



(i-b) (ii-b)

[0462] 包括下文方法和实施例中合适的其变体或替代形式。还描述了以其盐、外消旋体、非对映异构体、酯、氨基甲酸盐/酯、磷酸盐/酯、硫酸盐/酯、氘代形式和前药形式存在的本发明的组合物的制备。

[0463] 通用方法A

[0464] 本发明的化合物可在本领域技术人员熟悉的铃木(Suzuki)偶联条件下制备。合适的条件包括(i)将前体(包括硼酸或其硼酸酯)与中间体(包括卤素(特别是Cl、Br和I)或三氟)偶联(或反之亦然)；(ii)存在碱的条件下，如碳酸铯或碳酸钾；(iii)钯催化剂，如$Pd(dppf)Cl_2$或$Pd(PPh_3)_2Cl_2$；以及(iv)有机溶剂，如二噁烷或DMF。

[0465] 通用方法B

[0466] 本发明的化合物可通过在还原条件下将酮部分还原为仲醇来制备。合适的条件包括(i)还原剂，如$NaBH_4$；以及(ii)有机溶剂，如TMF。

[0467] 通用方法C

[0468] 包括二醇部分的本发明的化合物可通过在氧化条件下烯烃部分的氧化来制备。合适的条件包括(i)氧化剂，如OsO_4；以及(ii)有机溶剂，如吡啶。

[0469] 通用方法D

[0470] 包括二醇部分的本发明的化合物可在本领域技术人员熟悉的环氧环开环条件下制备。

[0471] 通用方法 E

[0472] 本发明的化合物可经由有机 - 金属加成，通过将醛部分烷基化成仲醇来制备。合适的条件包括 (i) 格氏试剂，如卤化（烷基）镁；以及 (ii) 有机溶剂，如 Et_2O。

[0473] 通用方法 F

[0474] 本发明的化合物可在本领域技术人员熟悉的史蒂勒 (Stille) 偶联条件下制备。合适的条件包括 (i) 将前体（包括卤素（特别是 Cl、Br 和 I)）与包括甲锡烷基化部分的中间体（如三丁基锡）偶联（或反之亦然）；(ii) 存在钯催化剂的条件下，如 $Pd(PPh_3)_4$；以及 (iii) 有机溶剂，如 DMF。

[0475] 通用方法 G

[0476] 本发明的化合物可在本领域技术人员熟悉的陈 - 林 (Chan-Lam) 偶联条件下制备。合适的条件包括 (i) 将包含 N-H 部分的前体与包括硼酸的中间体偶联（或反之亦然）；(ii) 存在铜试剂（如 $Cu(OAc)_2.H_2O$) 的条件下，在氧气气氛中。

[0477] 通用方法 H

[0478] 本发明的化合物（包含仲或叔醇部分的前药形式）可在本领域技术人员熟悉的合适条件下形成。前药形式包括氨基甲酸盐 / 酯、磷酸盐 / 酯和酯，包括来源于氨基酸和二糖的那些，其形成的合适条件如下文实施例中所述。

[0479] 通用方法 I

[0480] 本发明的化合物可在本领域技术人员熟悉的齐沃德 - 哈特威格 (Buchwald-Hartwig) 偶联条件下制备。合适的条件包括 (i) 将包括卤素的前体与包括 N-H 部分的中间体偶联（或反之亦然）；(ii) 存在钯催化剂的条件下，如 $Pd_2(dba)_3$；(iii) 合适的配体，如 Xantphos；(iv) 合适的碱，如 Cs_2CO_3；以及 (v) 有机溶剂，如 1,4- 二噁烷。

[0481] 盐的形成方法

[0482] 本发明的化合物的盐可使用本领域技术人员熟悉的条件制备，例如以下条件。通用的盐形成条件

[0483] 将游离碱材料溶解或悬浮于有机溶剂、有机溶剂混合物或有机溶剂水混合物（例如 DCM、THF、THF/MeOH、EtOH) 中，并添加等于或大于 1 摩尔当量溶解 / 悬浮于相同有机溶剂或有机溶剂混合物中的酸溶液 / 悬浮液。也可以净相形式添加酸。盐产物可在室温下沉淀，或者可在较高温度下完成添加，随后冷却以使盐产物沉淀。可在添加酸后加入抗溶剂（如己烷、正庚烷、乙酸异丙酯）以使盐产物沉淀，所述盐产物通过真空过滤收集并使用适当有机溶剂清洗。

[0484] 示例盐酸盐

[0485] 盐酸盐可通过例如将化合物悬浮在合适溶剂（如乙腈）中并添加水性 2M 盐酸溶液来制备。使用水稀释化合物随后除去溶剂以形成化合物的盐酸盐。

[0486] 示例甲磺酸盐

[0487] 甲磺酸盐可通过例如将化合物悬浮在合适溶剂（如乙腈）中并添加 1 当量的甲磺酸水溶液来制备。除去溶剂以形成化合物的甲磺酸盐。

[0488] 手性分离方法和合成

[0489] 本发明的化合物可在本领域技术人员熟悉的手性 HPLC 条件下分离成其非对映异构体或对映异构体。或者，可通过手性助剂（如封闭的氨基酸，例如 Boc- 缬氨酸）衍生化的

方式从其外消旋体中解析手性前体部分，通过合适的溶剂（如庚烷）中非对映异构体的分步结晶以及经由助剂切除（如树脂上或溶液中碱介导的切除）的对映异构前体的重建以分离手性前体部分。手性醇的对映异构体富集混合物的 Mitsonobu 型转化还可通过在三烷基化膦类（如三苯基膦）和二烷基偶氮二甲酸酯存在的情况下将醇与手性助剂（如氨基酸，例如 Boc- 缬氨酸）偶联并分步结晶上述富集的非对映异构体混合物的方式完成。

[0490] 保护基团

[0491] 反应过程中，可能需要保护很多部分。合适的保护基团是工业上熟知的，并且在很多参考文献中描述，如 Protecting Groups in Organic Synthesis(《有机合成中的保护基团》)，Greene T W，纽约的威利国际科学出版公司 (Wiley Interscience)，1981。应理解在反应过程期间除了保护诸如羟基和氨基的基团外，在本文所述任意反应条件下脲部分也需要保护，例如 5- 甲基 -1,3,5- 三嗪 -2- 酮。

[0492] 官能基团互换

[0493] 此外，应理解可对在本文所述任意反应条件下生产的本发明的化合物在本领域技术人员熟悉的合适条件下进行进一步的官能化。即，本领域技术人员应理解可通过羟基和羧基的官能基团互换提供丰富多样的化合物，包括但不限于卤素、醚、酮、羧酸、酯、碳酸酯、胺、酰胺、脲、氨基甲酸酯、硫酸酯、磺酰胺、磷酸酯、杂环、杂芳基、任选经取代的烷基链延伸物等。

实施例

[0494] 本领域技术人员应理解，除了具体描述的那些以外，还可以对本文所述的发明进行变化和修改。现在描述本发明，但不受下述实施例的限制。

[0495] 除非另有说明，否则实施例中所用缩写的含义如下：

[0496] 缩写

[0497] Ac: 乙酰基

[0498] ACN: 乙腈

[0499] cfus: 菌落形成单位

[0500] DCM: 二氯甲烷

[0501] DIPEA: N,N- 二异丙基乙胺

[0502] DMAP: N,N- 二甲基吡啶 -4- 胺

[0503] DMF: N,N- 二甲基甲酰胺

[0504] DMSO: 二甲亚砜

[0505] EtOAc: 乙酸乙酯

[0506] Et_2O: 二乙醚

[0507] EtOH: 乙醇

[0508] g: 克

[0509] h: 小时

[0510] H_2O: 水

[0511] HPLC: 高效液相色谱

[0512] IPA: 丙 -2- 醇

[0513] kg: 千克

[0514] L: 升

[0515] LCMS: 液相色谱质谱联用

[0516] LDA: 二异丙基胺基锂

[0517] M: 摩尔 / 升

[0518] mg: 毫克

[0519] min: 分钟

[0520] mL: 毫升

[0521] MeOH: 甲醇

[0522] mol: 摩尔

[0523] mmol: 毫摩尔

[0524] MS: 质谱

[0525] NBS: N- 溴代琥珀酰亚胺

[0526] NMP: 1- 甲基吡咯烷 -2- 酮

[0527] NMR: 核磁共振

[0528] $Pd(dppf)Cl_2$: [1,1′ - 双 (二苯基膦基) 二茂铁] 二氯化钯 (II),DCM 加合物

[0529] $Pd_2(dba)_3$ 三 (二亚苄基丙酮) 二钯 (0)

[0530] $Pd(PPh_3)_4$ 四 (三苯基膦) 钯 (0)

[0531] RT: 室温

[0532] THF: 四氢呋喃

[0533] TLC: 薄层色谱法

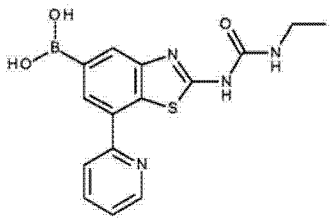
[0534] 化合物合成

[0535] 在 Brüker Avance DRX400、AC200 或 AM300 光谱仪上记录 ^1H NMR 谱图。使用残留溶剂峰作为参照在氘化溶剂 ($CDCl_3$、MeOD、DMSO-d_6、CD_3CN 或丙酮 -d_6) 中记录谱图。在 δ 等级以百万分之一 (ppm) 报告化学位移,使用下面惯例分配多重性 :s(单重)、d(双重)、t(三重)、q(四重)、p(六重)、m(多重) 和预先固定的 br(宽度)。在 Micromass Platform QMS 或 Thermo Finnigan LCQ Advantage 光谱仪上记录质谱 (ESI)。在 40-63μm 硅胶 60(默克公司 (Merck) 编号 9385) 上进行快速色谱。在使用 Combi-Flash™ 硅胶柱的 Combi-Flash™纯化系统上或者在使用 GraceResolv™ 硅胶管、Grace Reveleris™ C-18 反相硅胶管或 Biotage SNAP™ C-18 反相硅胶管的 Biotage SP4 纯化系统上进行自动快速色谱。使用装备了 Gilson215 液体处理器和 HP1100PDA 检测器的 Gilson322 泵或者使用 Varian XRs C-18 100x21.2mm 柱的 Agilent1200 系列质量检测的制备型 LCMS 进行制备型 HPLC。除非另有说明,否则,所述 HPLC 系统使用 Phenomenex C8(2) 柱,用乙腈或含有乙腈的以下溶液 :0.06% 的 TFA 水溶液、含 0.1% TFA 的水或含 0.1% 甲酸的水。

[0536] 中间体的实施例

[0537] [2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 硼酸 (中间体 1)

[0538]



^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.10 (t, J= 7.20 Hz, 3H), 3.20 (m, 2H), 6.84 (br s, 1H), 7.41 (m, 1H), 8.01 (m, 1H), 8.12 (s, 1H), 8.25 (m, 3H), 8.40 (s, 1H), 8.79 (d, J= 4.0 Hz, 1H) 和 10.57 (br s, 1H)。MS:343.25 $[M+H]^+$。

[0539] 2-氨基-3-溴-5-硝基-苯酚(i):在30min时间段内,向搅拌的2-氨基-5-硝基-苯酚(500g,3.24mol)的ACN(12L)溶液中逐滴加入溴(290mL,5.63mol)。将化合物在30-35℃下搅拌1小时,随后蒸发溶剂至干。加入己烷(2L)并蒸发混合物至干。加入己烷(5L)并将混合物搅拌1小时并过滤。用己烷(2L)洗涤固体(1102g)。所述残留物加入到冰水(2.5L)中,然后加入硫代硫酸钠饱和溶液(2.5L),并用EtOAc(2x10L)萃取。合并的有机层用盐水洗涤、干燥(Na_2SO_4)、过滤并在40-45℃下真空浓缩以获得i(643g,85%)。

[0540] 3-溴-5-硝基-苯酚(ii):在-10至-2℃下在35min时间段内,向i(643g,2.76mol)的EtOH(13L)冷却溶液(-10℃)中加入浓H_2SO_4(515mL,9.97mol)。使混合物升温至室温然后加热至50-55℃,随后在30min内逐份加入$NaNO_2$(671g,9.72mol)并在回流下将反应混合物加热3h。将混合物浓缩至3L并且冷却至0℃,然后加入冷水(5L)并用EtOAc(3x6L)萃取。合并的有机层用盐水洗涤、干燥(Na_2SO_4)、过滤并真空浓缩。残留物用25%醚-己烷混合物(6L)处理并且搅拌1h,过滤并用己烷(3L)洗涤以获得ii(505g,84%)。

[0541] 1-苄氧基-3-溴-5-硝基-苯(iii):室温下在30min时间段内,向ii(770g,3.53mol)的丙酮(10L)溶液中加入K_2CO_3(2.45kg,17.75mol),然后加入苄基溴(632mL,5.32mol)。混合物搅拌15min并在回流下加热3h。通过硅藻土过滤混合物并蒸馏除去丙酮。用二氧化硅纯化残留物并使用EtOAc:己烷(5:95)洗脱以获得iii(551g,51%)。

[0542] 3-苄氧基-5-溴-苯胺(iv):室温下向iii(551g,1.78mol)的THF(11L)溶液中加入$SnCl_2.2H_2O$(2.17kg,9.62mol)。将混合物回流3h。将混合物冷却到0-5℃并用饱和$NaHCO_3$溶液碱化,并用EtOAc(4x5L)萃取。合并的有机层用盐水洗涤、干燥(Na_2SO_4)、过滤并真空浓缩以得到iv(480g,97%)。

[0543] N-[(3-苄氧基-5-溴苯基)硫代氨甲酰基]苯甲酰胺(v):室温下向iv(480g,1.73mol)的丙酮(10L)溶液中加入苯甲酰异硫氰酸酯(280mL,2.08mol)并将混合物搅拌45min。蒸馏去除丙酮并添加己烷(2L)并将混合物浓缩至干。向残留物中加入己烷(4L)并将混合物加热30min至40℃。通过过滤收集固体并使用己烷(2x2L)清洗以获得v(648g,85%)。

[0544] (3-苄氧基-5-溴-苯基)硫脲(vi):室温下向v(648g,1.47mol)的THF(12L)溶液加入NaOH溶液(300g,7.5mol,3L水中)。将该混合物加热至70℃过夜。倾析出THF层,并用EtOAc(3x2L)萃取水性层。合并的有机层用盐水洗涤、干燥(Na_2SO_4)、过滤并真空浓缩。残留物用Et_2O和己烷的混合物(5:95,3.0L)处理,过滤,用己烷洗涤,并在高真空下干燥以获得vi(387g,78%)。

[0545] 5-苄氧基-7-溴-1,3-苯并噻唑-2-胺(vii):在30min时间段内,向vi(372g,1.10mol)的ACN(6L)冰冷悬浮液中逐滴加入溴溶液(50mL乙腈中65mL1.26mol)。在0-5℃下将混合物搅拌30min并随后缓慢升温至室温并搅拌1h。滤出固体并使用

己烷(2x3L)清洗。将固体残留物置于冰水中,用水性 NH_3(pH10-12)碱化且在5-10℃搅拌30min。滤除所得固体,用水洗涤,并且在高真空下干燥以获得vii(216g,59%)。^{1}H-NMR(DMSO-d_6,400MHz):δ5.12(s,2H),6.92(d,J = 2.40Hz,1H),6.98(d,J = 2.0Hz,1H),7.30-7.45(m,5H)和7.69(brs,2H)。MS:334.79[M+H]$^+$。

[0546] 1-(5-苄氧基-7-溴-1,3-苯并噻唑-2-基)-3-乙基-脲(viii):向vii(216g,0.64mol)的1,4-二噁烷(4L)悬浮液中加入乙基异氰酸酯(380mL,4.81mol)。将混合物加热到80-85℃过夜。蒸馏除去溶剂并用己烷共蒸发残留物。使用水在78-80℃下处理残留物3-5h。过滤掉所得固体并用热水洗涤,在高真空下干燥以获得viii(196g,75 %)。^{1}H-NMR(DMSO-d_6,400MHz):δ1.08(t,J = 7.20Hz,3H),3.18(q,J = 6.80Hz,2H),5.17(s,2H),6.71(br s,1H),7.15(d,J = 2.0Hz,1H),7.26(br s,1H),7.31-7.47(m,5H)和10.82(br s,1H)。MS:405.90[M+H]$^+$。

[0547] 1-[5-苄氧基-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲(ix):向搅拌的viii(110g,0.27mol)的DMF(1.1L)溶液中加入2-三丁基甲锡烷基吡啶(298g,0.81mol)。所得溶液用 N_2 吹扫15-20min,然后加入 $Pd(PPh_3)_4$(25.41g,0.022mol)。将所得反应混合物在 N_2 气氛下加热至100℃持续15-16h。使反应冷却至40-45℃并通过硅藻土过滤。用DMF(500mL)和热的EtOAc(1.50L)洗涤硅藻土,并在60-70℃真空浓缩结合的滤液。通过二氧化硅(20% EtOAc-己烷至100% EtOAc)纯化残留物以获得ix(76g,70 %)。^{1}H-NMR(DMSO-d_6,400MHz):δ1.08(t,J = 7.20Hz,3H),3.19(q,J = 6.80Hz,2H),5.26(s,2H),6.84(br s,1H),7.32-7.43(m,5H),7.51(d,J = 7.20Hz,2H),7.69(d,J = 2.0Hz,1H),7.95(m,1H),8.25(m,1H),8.78(m,1H)和10.46(br s,1H)。MS:405.30[M+H]$^+$。

[0548] 1-乙基-3-[5-羟基-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-脲(x):在30min时间内,向搅拌的ix(76g,0.187mol)的DCM(1.7L)溶液中逐滴加入甲磺酸(270mL,4.17mol)。室温搅拌该混合物3小时。对反应进行真空浓缩。将EtOAc(1L)加入到残留物中,并将该溶液仔细倒在压碎的冰上。加入饱和 $NaHCO_3$ 溶液将溶液pH调节至8-9,然后用EtOAc(3x5L)萃取。合并的有机层用水、盐水洗涤、干燥(Na_2SO_4)、过滤并真空浓缩。残留物在 Et_2O(1.0L)中RT搅拌1h,然后过滤以获得x(57.0g,97%)。^{1}H-NMR(DMSO-d_6,400MHz):δ1.08(t,J = 7.20Hz,3H),3.20(m,2H),6.86(br s,1H),7.0(s,1H),7.46(s,2H),7.96(m,1H),8.10(m,1H),8.76(m,1H),9.59(br s,1H)和10.41(br s,1H)。MS:315.06[M+H]$^+$。

[0549] [2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]三氟甲磺酸酯(xi):向搅拌的x(57g,0.181mol)的DMF(1.7L)溶液中加入N-苯基双(三氟甲磺酰亚胺)(80.74g,0.226mol)和DIPEA(28g,0.217mol)。室温下搅拌该混合物3h。反应在60-70℃下进行真空浓缩。将 Et_2O 加入到残留物中,并且蒸发至干。由此得到的残留物用 Et_2O(1.5L)搅拌1h,然后过滤以获得xi(55.0g,68%)。^{1}H-NMR(DMSO-d_6,400MHz):δ1.11(t,J = 7.20Hz,3H),3.20(m,2H),6.81(br s,1H),7.50(m,1H),7.78(d,J = 2.0Hz,1H),8.01(m,1H),8.12(d,J = 2.40Hz,1H),8.35(m,1H),8.84(m,1H)和10.77(br s,1H)。MS:446.98[M+H]$^+$。

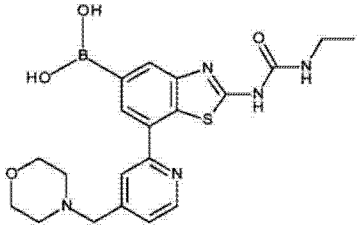
[0550] [2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]硼酸(中间体1):室温下向搅拌的xi(25g,56.1mmol)的DMSO(250mL)溶液中加入双(新戊基乙二醇)

(neopentylglycolato) 二硼 (25.2g,112mmol) 和 KOAc(16.5g,168mmol)。所得反应混合物通过 N_2 吹扫脱气 15-20min,然后加入 Pd(dppf)Cl_2(6.8g,8.4mmol)。混合物用 N_2 吹扫 15-20min,然后加热到 80℃持续 90min。将反应物倒在饱和 NH_4Cl 溶液 (1L) 上。所得沉淀过滤并真空下干燥。将固体块置于 2M NaOH(200mL) 中,并且室温搅拌 45min。过滤溶液并将滤液酸化至 pH5-6,并通过过滤收集所得固体以获得中间体 1(17g,88%)。

[0551] 使用类似方法制备以下中间体:

[0552] [2-(乙基氨甲酰基氨基)-7-[4-(吗啉基甲基)-2-吡啶基]-1,3-苯并噻唑-5-基]硼酸(中间体 2):

[0553]



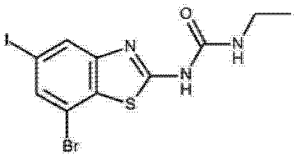
MS:413.13 $[M+H]^+$。

[0554] 以与中间体 1 类似的方法制备,不同之处在于将 C7 取代基添加至 1-(5-苄氧基-7-溴-1,3-苯并噻唑-2-基)-3-乙基-脲的步骤是在铃木 (Suzuki) 偶联条件而非史蒂勒 (Stille) 偶联条件下进行的,如下:

[0555] 1-[5-苄氧基-7-[4-(吗啉基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]-3-乙基-脲 (i):在DMSO(120mL) 中悬浮 1-(5-苄氧基-7-溴-1,3-苯并噻唑-2-基)-3-乙基-脲 (27.7g,68.3mmol)、2-(5,5-二甲基-1,3,2-二氧杂硼杂己环 (borinan)-2-基)-5,5-二甲基-1,3,2-二氧杂硼杂己环 (18.2g,80.7mmol) 和乙酸钾 (12.2g,124mmol) 的混合物。使用 N_2 气流对混合物脱气 15min。加入 Pd(dppf)Cl_2(5.07g,6.21mmol) 并在 85℃下加热混合物 6h,随后冷却至室温。加入前体 10(13.2g,62.1mmol) 的 DMSO(20mL) 溶液,随后加入 Cs_2CO_3(30.3g,93.1mmol) 和水 (30mL)。使用 N_2 气流对混合物脱气 10min。加入 Pd$(PPh_3)_2Cl_2$(4.36g,6.21mmol) 并在 85℃下加热混合物过夜。冷却溶液并用水 (400mL) 稀释,剧烈搅拌直至固体形成并弃去上清液。将固体悬浮在 EtOAc/DCM(300mL) 中并通过二氧化硅凝胶短塞过滤,使用 5-10% MeOH/DCM 洗脱。随后浓缩溶液,在 DCM(500mL) 中溶解并在使用 3M HCl(150mL) 室温搅拌 2 天。过滤收集沉淀,使用 DCM 和水清洗。将得到的固体材料悬浮在 EtOAc/DCM(200mL) 中,超声并通过过滤收集固体以获得 I(25.5g)。MS:504.17 $[M+H]^+$。

[0556] 1-(7-溴-5-碘-1,3-苯并噻唑-2-基)-3-乙基-脲(中间体 3)

[0557]



^{1}H NMR (DMSO-d_6,400 MHz): δ 1.08 (t, J= 7.20 Hz, 3H), 3.20 (q, J= 6.80, 2H), 6.73 (br s, 1H), 7.72 (s, 1H), 7.96 (s, 1H) 和 11.07 (br s, 1H)。MS:426.0 $[M+H]^+$。

[0558] 2-溴-4,6-二硝基苯胺 (i):室温下,在 30min 内,向搅拌的水 (3.75L) 和乙酸 (375mL) 的混合物中加入 2,4-二硝基苯胺 (500g,2.73mol),然后逐滴加入溴 (210mL,4.09mol)。将反应混合物室温搅拌 15min,随后加热至 100℃持续 2h。将反应物冷却至室温并倒在冰水 (5-6L) 上并用氨水碱化 (pH8-10)。过滤固体,用冷水洗涤并在真空下

干燥。使用正戊烷洗涤该固体以获得 i(600g,84%)。

[0559] 1,2-二溴-3,5-二硝基苯(ii):室温下向搅拌的 i(600g,2.28mol)的 ACN(5L)的溶液中加入亚硝酸叔丁酯(680mL,5.7mol)和溴化铜(767g,3.43mol)。将混合物在 N_2 下加热到 70℃持续 1h。反应冷却到室温,用 1M HCl 溶液酸化,加入水(4L),并用 EtOAc(3x4L)萃取。对合并的有机层进行干燥(Na_2SO_4),过滤并真空浓缩以获得 ii(723g,97%)。^{1}H NMR($CDCl_3$,400MHz):δ8.48(d,J=2.40Hz,1H)和 8.68(d,J=2.40Hz,1H)。

[0560] (2-溴-4,6-二硝基-苯基)硫氰酸酯(iii):室温下向搅拌的 ii(723g,2.22mol)的 MeOH(7.5L)溶液中加入硫氰酸钾(431g,4.44mol)并将混合物在 N_2 下搅拌 16h。对反应进行过滤并使用 MeOH 洗涤。真空浓缩滤液。在二氧化硅(2-6% EtOAc-己烷)上纯化残留物以获得 iii(549g,81%)。

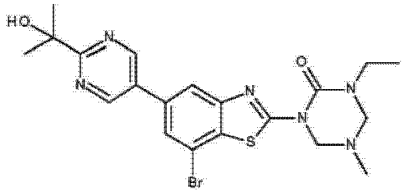
[0561] 7-溴苯并噻唑-2,5-二胺(iv):室温下向搅拌的 EtOH(8.37L)和水(8.37L)的混合物中加入 iii(549g,1.81mol),然后加入 Fe 粉(2.02kg,36.11mol)并在 30 分钟内逐滴加入 HCl(12N,527mL)。将混合物室温搅拌 20min,然后加热到 80℃持续 45min。将反应物冷却至室温,通过加入氨水溶液碱化至 pH8-10。使溶液通过硅藻土,用 EtOAc 洗涤,并真空蒸发合并的滤液。加入水(8L)并使用 EtOAc(2x4L)萃取。合并的有机层用盐水洗涤、干燥(Na_2SO_4)、过滤并真空浓缩以获得 iv(412g,93%)。^{1}H NMR(DMSO-d_6,400MHz):δ5.16(br s,2H),6.50(d,J=2.0Hz,1H),6.53(d,J=1.60Hz,1H)和 7.44(br s,2H)。MS:243.86$[M+H]^+$。

[0562] 7-溴-5-碘苯并噻唑-2-胺(v):在-78℃和 N_2 气氛下,向 THF(6L)中加入 BF3-醚合物(50%试样,708mL,2.81mol),然后在 20min 内,缓慢加入 iv(275g,1.02mol)的 THF(500mL)溶液。随后在-78℃下向溶液中加入亚硝酸叔丁酯(548L,4.61mol)并在同一温度下将混合物搅拌 40min,随后升温至-5 至 0℃。(在-5-0℃下)加入 Et_2O 并搅拌混合物 20min。在 0℃下过滤固体并置于丙酮中,随后依次加入 KI(510g,3.07mol)和碘(519g,2.04mol),并且 0℃下搅拌混合物 30min。使用偏亚硫酸氢钠的饱和溶液终止反应并使用 EtOAc(3x5L)萃取。对合并的有机层进行干燥(Na_2SO_4)、过滤并 45℃下真空浓缩。碱性氧化铝(30-35% EtOAc-己烷)上纯化残留物以获得 v(235g,65%)。^{1}H NMR(DMSO-d_6,400MHz):δ7.50(d,J=1.20Hz,1H),7.63(d,J=1.20Hz,1H)和 7.91(br s,2H)。MS:354.90$[M+H]^+$。

[0563] 1-(7-溴-5-碘苯并噻唑-2-基)-3-乙基脲(中间体 3):室温下向搅拌的 vi(250g,0.70mol)的 1,4-二噁烷溶液中加入乙基异氰酸酯(278mL,3.52mol)。将混合物在 N_2 下加热到 80℃持续 10-12h。蒸发溶剂,加入正己烷并将混合物浓缩至干。残留物在热水(2L)中于 60-65℃搅拌 30-40min,然后过滤。随后用 Et_2O 和正戊烷的混合物处理残留物,过滤以获得中间体 3(264g,88%)。

[0564] 1-[7-溴-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-5-甲基-1,3,5-三嗪-2-酮(中间体 4)

[0565]



^{1}HNMR (DMSO-d_6 400 MHz)：δ 9.20 (s, 2H), 8.13 (s, 1H), 7.91 (s, 1H), 5.14 (m, 3H), 4.39 (s, 2H), 3.36 (q, J= 7.20 Hz, 2H), 2.54 (s, 3H), 1.53 (s, 6H) 和 1.12 (t, J= 7.20 Hz, 3H)。

[0566] 2-(5-溴嘧啶-2-基)丙-2-醇)(i)：在30min内，向冰冷的5-溴嘧啶-2-羧酸酯(10g,46.1mmol)的Et_2O(200mL)溶液中逐滴加入甲基溴化镁(3.0M溶解在Et_2O，61.4mL中，184mmol)将反应混合物缓慢升温至室温并持续搅拌2h。在0℃下使用饱和的NH_4Cl溶液终止混合物，并从双相溶液中分离有机层。用EtOAc(2x250mL)再次萃取水层。用盐水溶液洗涤合并的有机层，用Na_2SO_4干燥，过滤并在真空中浓缩。在二氧化硅上纯化粗残留物，使用20％EtOAc：己烷洗脱以获得i(6.0g,62％)。^{1}HNMR(DMSO-d6,400MHz)：δ8.97(s,2H),5.15(s,1H)和1.47(s,6H)。

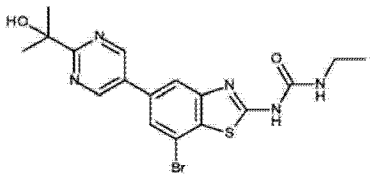
[0567] 2-(5-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷(dioxaborolan)-2-基)嘧啶-2-基)丙-2-醇(ii)：向i(6.0g,27.6mmol)的1,4-二噁烷(60mL)溶液中加入双(频哪醇合)二硼(8.42g,33.2mmol)和KOAc(4.06g,41.5mmol)。反应物通过N_2吹扫脱气15min。向脱气10min的反应混合物中加入$Pd_2(dba)_3$(1.43g,1.4mmol)和三环己基膦(0.93g,3.31mmol)。将得到的反应混合物在80℃下加热2h。将混合物冷却至室温并通过硅藻土床过滤。真空浓缩滤液以获得ii(5.11g,70％)。MS:265.13$[M+H]^+$。

[0568] 1-(7-溴-5-(2-(2-羟基丙-2-基)嘧啶-5-基)苯并[d]噻唑-2-基)-3-乙基-5-甲基-1,3,5-三嗪-2-酮(中间体4)：室温下向中间体3(7.50g,15.48mmol)和ii(5.11g,19.36mmol)的1,4-二噁烷:MeOH(75:50mL)溶液中刚加入磷酸钾(6.15g,29.03mmol)。所得混合物用N_2吹扫15-20min以脱气，然后加入$Pd(PPh_3)_4$(2.23g,1.93mmol)。反应混合物再次脱气15-20min，然后加热到80℃持续5h。将混合物冷却至室温并通过硅藻土床并使用EtOAc洗涤。真空蒸发滤液并在二氧化硅上纯化残留物，使用3％MeOH:DCM洗脱以获得中间体4(7.50g,97％)。

[0569] 使用类似方法制备以下中间体。

[0570] 1-[7-溴-5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-3-乙基-脲(中间体5)

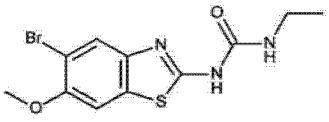
[0571]



MS:437.91 $[M+H]^+$。

[0572] 1-(5-溴-6-甲氧基-1,3-苯并噻唑-2-基)-3-乙基-脲(中间体6)

[0573]



MS:329.94 和 331.91 $[M+H]^+$。

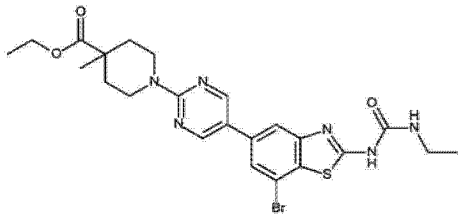
[0574] 1-乙基-3-(6-甲氧基-1,3-苯并噻唑-2-基)脲(i)：在无水DMSO(20mL)和三乙基胺(15.5mL,111mmol)中溶解6-甲氧基-1,3-苯并噻唑-2-胺(5.0g,27.7mmol)，然

后加入异氰酸乙酯 (4.39mL,55.5mmol)。在 N_2 和室温下搅拌混合物 4h,随后使用水 (～ 200mL) 终止反应并搅拌 1h。过滤收集所得白色固体并使用水然后使用丙酮 (100mL) 清洗并将滤液单独收集成水性滤液。将滤液真空浓缩至干,并与过滤得到的固体合并以获得 i(6.27g,90%)。MS:251.96[M+H]$^+$。

[0575] 1-(5- 溴 -6- 甲氧基 -1,3- 苯并噻唑 -2- 基)-3- 乙基 - 脲 (中间体 6) :在 DCM(50mL) 和 MeOH(5mL) 中悬浮化合物 i(1.10g,4.38mmol) 并加入溴 (0.34mL,6.60mmol)。将混合物室温搅拌 1.5h,随后真空浓缩至干以形成中间体 6(2.17g)。

[0576] 1-[5-[7- 溴 -2-(乙基氨甲酰基氨基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基]-4- 甲基 - 哌啶 -4- 羧酸乙酯 (中间体 7)

[0577]



^{1}H NMR (DMSO-d_6 400 MHz):δ 1.09 (t, J= 7.20 Hz, 3H), 1.20 (m, 6H), 1.45 (m, 2H), 2.03 (m, 2H), 3.16 (m, 2H), 3.30 (q, J=7.20, 2H), 4.12 (q, J= 6.80 Hz, 2H), 4.25 (m, 2H), 6.75 (br s, 1H), 7.69 (s, 1H), 7.86 (s, 1H); 8.75 (s, 2H) 和10.91 (br s, 1H)。MS:547.11 [M+H]$^+$。

[0578] O1- 叔丁基 O4- 乙基 4- 甲基哌啶 -1,4- 二羧酸酯 (i) :将 O1- 叔丁基 O4- 乙基哌啶 -1,4- 二羧酸酯 (1.5g,5.84mmol) 的 THF(25mL) 溶液冷却到 - 78℃,然后 - 78℃下逐滴加入 LDA(1.80M 溶解于 THF,6.5mL 中,11.68mmol)。在 -78℃将得到的混合物搅拌 45min,随后加入甲基碘 (1.2mL,17.52mmol)。将温度缓慢升至室温并在室温维持 6h。将反应冷却至 0℃并逐滴加入饱和的 NH_4Cl 溶液 (50mL) 以终止反应。反应使用 EtOAc(3x100mL) 进行萃取。合并的有机层用盐水洗涤、干燥 (Na_2SO_4)、过滤并真空浓缩。在二氧化硅上通过色谱纯化并使用含 2% EtOAc 的己烷洗脱以得到 i(1.0g,65%)。

[0579] 盐酸 4- 甲基哌啶 -4- 羧酸乙酯 (ii) :向冰冷的 i(1g,3.68mmol) 的 1,4- 二噁烷 (10mL) 溶液中加入 HCl-1,4- 二噁烷 (4.0M,15mL) 溶液并室温搅拌 30min。蒸发溶剂以获得 ii(0.90g)。MS:172.16[M+H]$^+$。

[0580] 1-(5- 溴嘧啶 -2- 基)-4- 甲基哌啶 -4- 羧酸乙酯 (iii) : 室温下向 ii(0.9g,4.35mmol) 的 EtOH(10mL) 溶液中加入 DIPEA(1.92mL,13mmol) 并将混合物室温搅拌 10min,然后加入 5- 溴 -2- 氯嘧啶 (0.7g,3.6mmol)。将混合物在 70℃下加热 1h。蒸发溶剂并在二氧化硅上通过色谱纯化粗残留物,使用 1.5% EtOAc: 己烷洗脱以获得 iii(0.90g,75 %)。^{1}H NMR(DMSO-d_6,400MHz) : δ 1.17(s,3H),1.21(t,J = 7.20Hz,3H)1.40(m,2H),2.00(m,2H),3.24(m,2H),4.11(m,2H),4.15(q,J = 7.20Hz,2H),8.43(s,2H)。MS:328.08[M+H]$^+$。

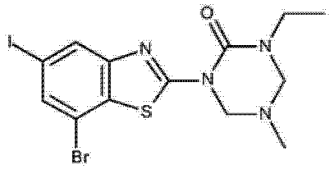
[0581] 4- 甲基 -1-(5-(4,4,5,5- 四甲基 -1,3,2- 二氧杂环戊硼烷 -2- 基) 嘧啶 -2- 基) 哌啶 -4- 羧酸乙酯 (iv) :向 iii(25g,76.2mmol) 的 1,4- 二噁烷 (250mL) 溶液中加入乙酸钾 (22.4g,228.6mmol) 和双 (频哪醇合) 二硼 (38.7g,152.4mmol)。用 N_2 吹扫混合物 15-20min 进行脱气,然后加入 $Pd_2(dba)_3$(4.0g,3.80mmol) 和三环己基磷 (2.55gm,9.12mmol)。混合物再脱气 15-20min,然后加热到 80℃持续 3h。将混合物冷却至室温并使用 500mL EtOAc 稀释并使其通过硅藻土床。蒸发滤液以获得 iv(20g,70%)。MS:376.30[M+H]$^+$。

[0582] 1-[5-[7- 溴 -2-(3- 乙基脲基) 苯并噻唑 -5- 基] 嘧啶 -2- 基]-4- 甲基哌啶 -4- 羧

酸乙酯（中间体 7）：室温下向中间体 3(22.7g,53.2mmol) 和 iv(20g,53.2mmol) 的 1,4- 二噁烷 :MeOH(300:180mL) 溶液中加入磷酸钾 (17g,79mmol)。所得混合物用 N_2 吹扫 15-20min 以脱气，然后加入 $Pd(PPh_3)_4$(6.1g,5.32mmol)。反应混合物再脱气 15-20min，然后加热到 80℃持续 5h。将反应混合物冷却至室温并使用 EtOAc(500mL) 稀释并通过硅藻土床。蒸发滤液并在二氧化硅上通过色谱纯化粗残留物，使用 1.5% MeOH:DCM 洗脱以获得中间体 7(12g,41%)。

[0583] 1-(7- 溴 -5- 碘苯并 [d] 噻唑 -2- 基)-3- 乙基 -5- 甲基 -1,3,5- 三嗪 -2- 酮（中间体 8）

[0584]

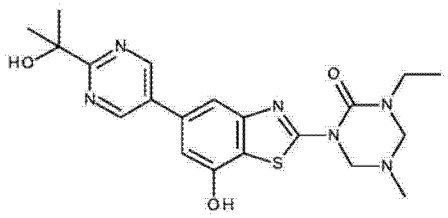


^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.11 (t, J= 7.20 Hz, 3H), 2.50 (s, 3H), 3.35 (m, 2H), 4.37 (s, 2H), 5.07 (s, 2H), 7.48 (s, 1H), 8.01 (s, 1H)。

[0585] 向中间体 3(50g,117.37mmol) 的 MeOH(1L) 溶液中加入甲醛 (37%水溶液，95mL)、甲基胺 (THF 中的 2M 溶液，587mL，1.17mol) 和 N- 甲基吗啉 (130mL,1.17mmol)。所得溶液在 75℃搅拌 5-6h。真空蒸发 MeOH。随后加入冰冷的水并将混合物搅拌 30min，然后过滤。先使用冷水随后使用正己烷和 EtOAc 洗涤残留物。高压干燥残留物以得到中间体 8(56g，定量)。

[0586] 1- 乙基 -3-[7- 羟基 -5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-5- 甲基 -1,3,5- 三嗪 -2- 酮（中间体 9）

[0587]



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.83 (s, 2H), 7.34 (s, 1H), 6.82 (s, 1H), 5.07 (s, 2H), 4.63 (s, 1H), 4.21 (s, 2H), 3.37 (q, J = 7.0 Hz, 2H), 2.55 (s, 3H), 1.52 (s, 6H), 1.13 - 1.08 (m, 4H)。MS:429 $[M+H]^+$。

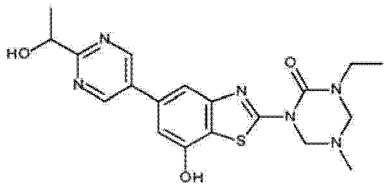
[0588] [2-(3- 乙基 -5- 甲基 -2- 氧代 -1,3,5- 三嗪 -1- 基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 基] 硼酸 (i)：将中间体 4(500mg)、乙酸钾 (300mg)、双（新戊基乙二醇）二硼 (460mg) 和 $Pd(dppf)_2Cl_2$(70mg) 在甲苯 (10mL) 中的混合物在真空下脱气 (x3)，随后在 130℃加热 90min。冷却混合物并通过硅藻土过滤。浓缩滤液以得到 i(465mg)。MS:457.02$[M+H]^+$。

[0589] 1- 乙基 -3-[7- 羟基 -5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -2- 基]-5- 甲基 -1,3,5- 三嗪 -2- 酮（中间体 9）：将化合物 ii(465mg) 的丙酮 (5mL) 溶液冷却至 0℃，随后用过硫酸氢钾制剂 (940mg) 的饱和 $NaHCO_3$(35mL) 溶液逐滴处理。反应室温搅拌过夜，随后加入过硫酸氢钾制剂 (100mg) 的饱和 $NaHCO_3$(5mL) 溶液。使用 1M HCl 中和混合物并使用 4:1DCM:IPA(3x30mL) 萃取。用盐水 (20mL) 洗涤有机萃取物，随后浓缩。将残留物悬浮于 5% MeOH:DCM 中，并在二氧化硅上通过色谱纯化，使用 0-10% MeOH:DCM 洗脱以得到中间体 9(240mg)。

[0590] 使用类似方法制备以下中间体。

[0591] 1-乙基-3-[7-羟基-5-[2-(1-羟基乙基)嘧啶-5-基]-1,3-苯并噻唑-2-基]-5-甲基-1,3,5-三嗪-2-酮(中间体10)：

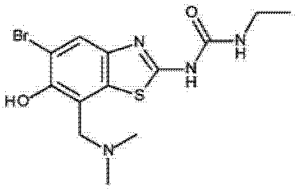
[0592]



MS:415.1 $[M+H]^+$。

[0593] 1-[5-溴-7-(二甲基氨基甲基)-6-羟基-1,3-苯并噻唑-2-基]-3-乙基-脲(中间体11)：

[0594]



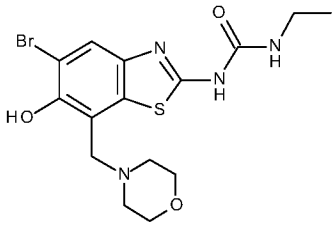
MS 372.89和374.87 $[M+H]^+$。

[0595] 1-(5-溴-6-羟基-1,3-苯并噻唑-2-基)-3-乙基-脲(i)的制备：将中间体6(1.30g,3.94mmol)悬浮在溴化氢溶液(6.82mL,47%水溶液,59.1mmol)中,并将所得悬浮液升温至110℃。在反应过程中逐份加入溴化氢溶液(14mL,47%水溶液,121.3mmol)。47h后,将反应混合物冷却至室温随后置于冰中,使用氢氧化钠溶液(1M水溶液)将pH调节至pH8。过滤该混合物并用水和ACN洗涤所得固体。吸干固体以得到i(1.01g,81%)。MS315.87和317.84$[M+H]^+$。

[0596] 1-[5-溴-7-(二甲基氨基甲基)-6-羟基-1,3-苯并噻唑-2-基]-3-乙基-脲(中间体11)：向i(209mg,0.66mmol)的DMF(2mL)混合物中加入三乙基胺(0.14mL,0.99mmol),随后加入N,N-二甲基甲基氯烯亚胺(dimethylmethyleneiminium chlorde)(147mg,0.79mmol)。在室温下搅拌该混合物。4.25h后,加入更多的N,N-二甲基甲基氯烯亚胺(～10mg)并持续搅拌。6h后,使用N_2气流蒸发溶剂。将残留物悬浮在DCM(～10mL)中并通过PTFE滤纸过滤。使用DCM(～15ml)洗涤固体,并真空浓缩滤液以形成油状物。通过色谱纯化油状物,在二氧化硅上使用含0-5% MeOH的DCM洗脱以得到中间体11(176mg,71%)。

[0597] 1-[5-溴-6-羟基-7-(吗啉基甲基)-1,3-苯并噻唑-2-基]-3-乙基-脲(中间体12)：

[0598]



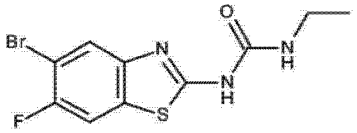
MS 414.93和416.91 $[M+H]^+$。

[0599] 在氩气下将多聚甲醛(29mg,0.05mmol)悬浮于无水DMF(2mL)中,并加入吗啉(0.08mL,0.95mmol)。将混合物在室温搅拌10min,随后加入中间体6(200mg,0.63mmol)。将混合物室温搅拌过夜,加热至90℃持续2h,随后冷却至室温。用水稀释混合物并形成沉

淀。加入 EtOAc 但沉淀仍维持不溶。通过 PTFE 滤纸过滤悬浮液并使用水和 EtOAc 清洗固体。用 EtOAc(4x20mL) 萃取两相滤液。合并的有机层用水 (3x50mL) 洗涤，干燥 (Na_2SO_4) 并真空浓缩。通过色谱纯化材料，在二氧化硅上使用含 0-10% MeOH 的 DCM 洗脱以得到中间体 12(28mg, 11%)。

[0600] 1-(5-溴-6-氟-苯并噻唑-2-基)-3-乙基-脲(中间体 13)：

[0601]



^{1}H-NMR (400 MHz, DMSO-d_6):δ 1.08 (t, J= 6.80 Hz, 3H), 3.17 (m, 2H), 6.69(br s, 1H), 7.92 (d, J= 6.40 Hz, 1H), 8.0 (d, J= 8.40 Hz, 1H) 和 10.86 (br s, 1H)。

[0602] 1-苯甲酰-3-(5-溴-2,4-二氟-苯基)-硫脲 (i)：向 5-溴-2,4-二氟-苯胺 (1.0g, 4.81mmol) 的丙酮 (25.0mL) 溶液中逐滴加入苯甲酰异硫氰酸酯 (0.71mL, 5.29mmol)，并将混合物在室温搅拌 30min。蒸发溶剂并使用己烷和 Et_2O 洗涤残留物以得到 i(1.70g)。^{1}H-NMR(400MHz, $CDCl_3$)：δ 7.02-7.06(m, 1H), 7.56(t, J = 8.0Hz, 2H), 7.68(t, J = 7.60Hz, 1H), 7.91(d, J = 7.60Hz, 2H), 8.67(t, J = 7.60Hz, 1H), 9.15(br s, 1H) 和 12.65(br s, 1H)。

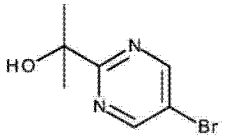
[0603] (5-溴-2,4-二氟-苯基)-硫脲 (ii)：向 i(1.70g, 4.60mmol) 的 THF(35.0mL) 溶液加入 NaOH(0.97g, 24.25mmol) 的水 (13.0mL) 溶液。将混合物在 70℃搅拌 15h。蒸发 THF、加入水并使用 EtOAc(3x50mL) 萃取混合物。合并的有机物用盐水洗涤并浓缩以获得 ii(1.0g, 83%)。MS267.03$(M+H)^+$。

[0604] 5-溴-6-氟-苯并噻唑-2-基胺 (iii)：向 ii(0.75g, 2.80mmol) 的 NMP(5.0mL) 溶液中逐份加入 NaH(0.17g, 4.21mmol，油中 60% 分散体)。混合物在 130℃加热 2h，随后倒在碎冰上并使用 EtOAc(3x50mL) 萃取。蒸发合并的有机物。在二氧化硅上通过色谱纯化并使用 12% EtOAc-己烷洗脱以得到 iii(0.36g, 52%)。^{1}H-NMR(400MHz, DMSO-d_6)：δ 7.57(d, J = 6.40Hz, 1H), 7.66(br s, 2H) 和 7.79(d, 8.80Hz, 1H)。

[0605] 1-(5-溴-6-氟-苯并噻唑-2-基)-3-乙基-脲(中间体 13)：向 iii(0.36g, 1.45mmol) 的 1,4-二噁烷 (25.0mL) 溶液中加入异氰酸乙酯 (0.69mL, 8.74mmol)，并将混合物在 80℃加热 15h。蒸发溶剂并将残留物在 60℃的水中搅拌 5h。过滤溶液并使用 Et_2O 洗涤以获得中间体 13(0.30g, 69%)。

[0606] 前体的实施例

[0607]

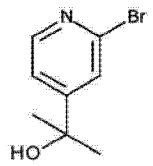
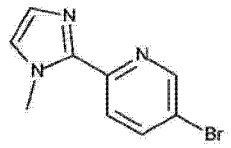
2-(5-溴嘧啶-2-基)丙-2-醇 （前体 1）		^{1}H NMR ($CDCl_3$,400 MHz):δ 8.8 (s, 2H), 4.3 (s, 1H), 1.6 (s 6H)。MS:218.78 $[M+H]^+$。

[0608] 将 5-溴嘧啶-2-羧酸乙酯 (500mg) 置于 Et_2O(10mL) 中并将混合物冷却至 0℃。逐滴加入甲基溴化镁 (3M, Et_2O 中)(1.32mL)，使反应升温至室温并搅拌 30min。加入 Na_2CO_3 溶液(饱和水溶液，2mL) 终止反应，用水 (50mL) 稀释，并用 EtOAc(2x50mL) 萃取。干燥 ($MgSO_4$) 合并的有机相并真空浓缩。在二氧化硅上通过色谱纯化，使用 0-100% 梯度的 EtOAc 的己烷

洗脱以得到前体 1(256mg)。

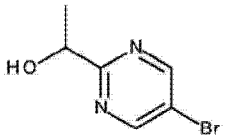
[0609] 使用类似方法制备以下前体。

[0610]

2-(2-溴-4-吡啶基)丙-2-醇 （前体2）	 MS:216和218 $[M+H]^+$。
5-溴-2-(1-甲基咪唑-2-基)吡啶 （前体3）	 MS:270 $[M+H]^+$。

[0611] 将含 THF(2.5mL) 中的 5- 溴 -2- 碘 - 吡啶 (500mg) 的烧瓶冷却至 -5℃。缓慢加入异丙基氯化镁 (2M,THF 中)(0.92mL) 并将反应搅拌 50min。加入 1- 甲基咪唑 -2- 醛 (288mg) 并将混合物搅拌 3h。将混合物冷却至 0℃,并加入 2M HCl 直至 pH ～ 7,随后加入水 (2mL) 和甲苯 (10mL),并收集和浓缩有机层。其在 EtOAc 和水之间分层,干燥 ($MgSO_4$) 并浓缩有机层。从 EtOAc 中结晶残留物以获得前体 3(150mg)。

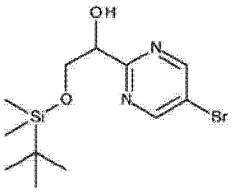
[0612]

1-(5-溴嘧啶-2-基)乙醇 （前体 4）	 MS:204.8 $[M+H]^+$。

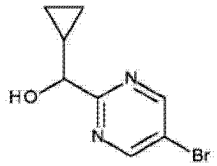
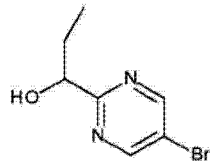
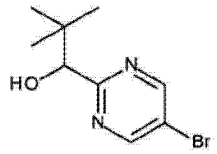
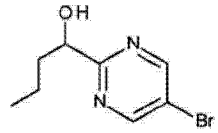
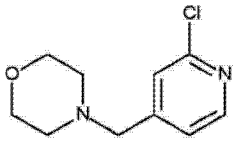
[0613] 在 -78℃下将 5- 溴 -2- 碘 - 嘧啶 (1g) 溶解在 THF(15mL) 中并加入氯化 (甲基) 镁 (3M, Et2O 中,2.34mL),随后将混合物在 -78℃下搅拌 30min。向所得溶液中逐滴加入乙醛 (0.60mL) 并在 30min 内搅拌反应同时使其升温至 0℃。加入 MeOH 并真空浓缩混合物。将所得固体溶解在 DCM/IPA(5:1 ;80mL) 中并用盐水 (50mL) 洗涤。在二氧化硅上通过色谱纯化,使用含 0-20% EtOAc 的庚烷洗脱以得到前体 4(244mg)。

[0614] 使用类似方法制备以下前体。

[0615]

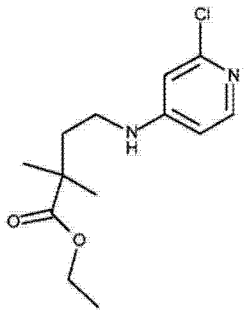
1-(5-溴嘧啶-2-基)-2-[叔丁基(二甲基)甲硅烷基]氧-乙醇 （前体5）	

[0616]

	MS:332.9和334.9, 1:1 $[M+H]^+$。
(5-溴嘧啶-2-基)-环丙基-甲醇 **（前体6）**	 MS:228.8 $[M+H]^+$。
1-(5-溴嘧啶-2-基)丙-1-醇 **（前体7）**	 MS:216.9 $[M+H]^+$。
1-(5-溴嘧啶-2-基)-2,2-二甲基-丙-1-醇 **（前体8）**	 MS:244.9 $[M+H]^+$。
1-(5-溴嘧啶-2-基)丁-1-醇 **（前体9）**	 MS:230.9 $[M+H]^+$。
2-氯-4-吗啉基甲基吡啶 **（前体10）**	

[0617] 向 2-氯-4-(氯甲基)吡啶(10g)的 THF(200mL)溶液中加入吗啉(5.94mL)和 K_2CO_3(18.8g)。将混合物室温下搅拌 3 天。反应进行过滤,使用 EtOAc 洗涤固体,并浓缩滤液。在二氧化硅塞(0-50% EtOAc/DCM)上纯化该材料以获得前体 10(6.87g)。

[0618]

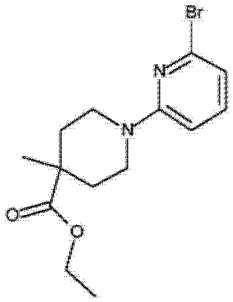
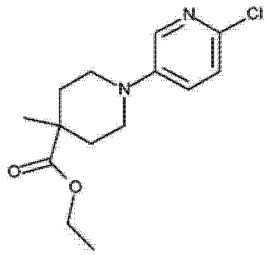
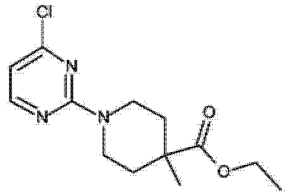
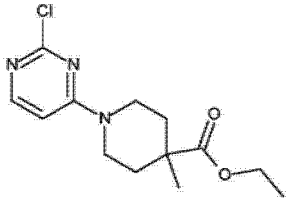
1-(2-氯-4-吡啶基)-4-甲基-哌啶-4-羧酸乙酯 **（前体11）**		^{1}H NMR (400 MHz, DMSO-d_6):δ 7.91 (d, J= 5.60 Hz, 1H), 6.81-6.83 (m, 2H), 4.10 (q, J= 6.80 Hz, 2H), 3.64-3.70 (m, 2H), 3.01-3.08 (m, 2H), 1.97-2.01 (m, 2H), 1.39-1.46 (m, 2H) 和 1.16-1.23 (m, 6H)。

[0619] 向 4-溴-2-氯-吡啶(2.0g,10.39mmol)的 EtOH(25mL)溶液中加入

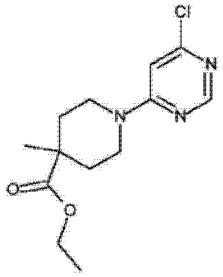
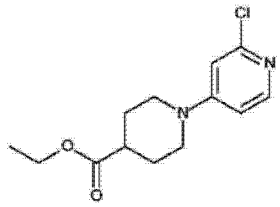
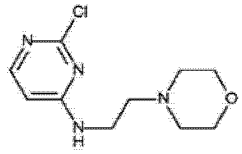
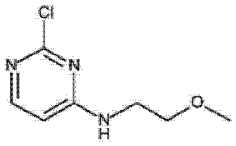
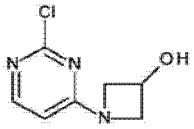
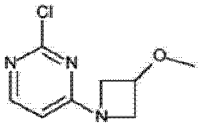
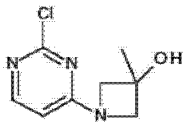
DIPEA(5.50mL,31.17mmol),随后加入盐酸 4- 甲基哌啶 -4- 羧酸乙酯 (2.60g,12.50mmol)。将所得反应混合物加热到 85℃持续 16h。蒸发溶剂并在二氧化硅上纯化残留物,使用 20% EtOAc- 己烷洗脱以获得前体 11(1.80g,75%)。

[0620] 使用类似方法制备以下前体。

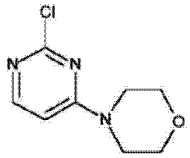
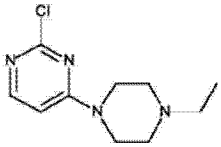
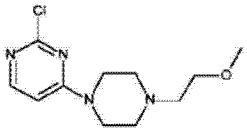
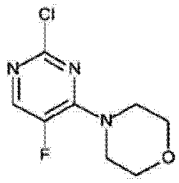
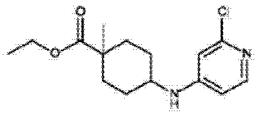
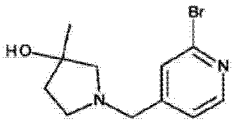
[0621]

1-(6-溴-2-吡啶基)-4-甲基-哌啶-4-羧酸乙酯 **(前体12)**		MS:327.0 $[M+H]^+$.^{1}H NMR (400 MHz, $CDCl_3$):δ 7.22 (s, 1H), 6.70 (d, *J*= 7.60 Hz, 1H), 6.51 (d, *J*= 8.40 Hz, 1H), 4.16 (q, *J*= 6.80 Hz, 2H), 3.88-3.94 (m, 2H), 3.07-3.14 (m, 2H), 2.15-2.18 (m, 2H), 1.43-1.50 (m, 2H) 和1.22-1.28 (m, 6H).
1-(6-氯-3-吡啶基)-4-甲基-哌啶-4-羧酸乙酯 **(前体13)**		MS 283.11 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6):δ 8.14 (d, *J*= 2.40 Hz, 1H), 7.63 (dd, *J*= 2.40 and 9.20 Hz, 1H), 6.81 (d, J= 9.20 Hz, 1H), 4.10 (q, *J*= 7.20 Hz, 2H), 3.84-3.89 (m, 2H), 3.05-3.12 (m, 2H), 1.96-2.0 (m, 2H), 1.36-1.43 (m, 2H) 和 1.16-1.20 (m, 6H).
1-(4-氯嘧啶-2-基)-4-甲基-哌啶-4-羧酸乙酯 **(前体14)**		MS 284.19 $[M+H]^+$.^{1}H NMR (400 MHz, $CDCl_3$):δ 8.0 (d, *J*= 6.40 Hz, 1H), 6.37 (d, *J*= 6.40 Hz, 1H), 4.20 (q, *J*= 6.80 Hz, 2H), 4.11 (m, 2H), 3.13-3.20 (m, 2H), 2.19-2.22 (m, 2H), 1.40-1.48 (m, 2H) 和 1.24-1.29 (m, 6H).
1-(2-氯嘧啶-4-基)-4-甲基-哌啶-4-羧酸乙酯 **(前体15)**		MS 284.05 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6):δ 8.05 (d, *J*= 6.0 Hz, 1H), 6.85 (d, *J*= 5.60 Hz, 1H), 4.13 (q, *J*= 7.20 Hz, 2H), 3.99 (m, 2H), 3.15-3.21 (m, 2H), 1.98-2.02 (m, 2H), 1.38-1.45 (m, 2H) 和 1.17-1.22 (m, 6H).

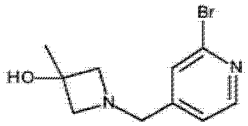
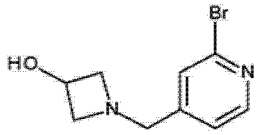
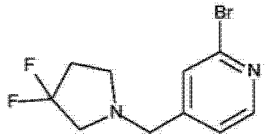
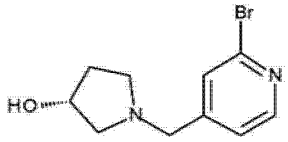
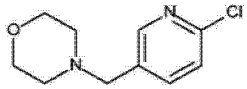
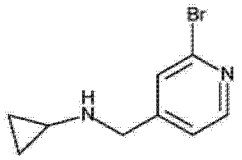
[0622]

1-(6-氯嘧啶-4-基)-4-甲基-哌啶-4-羧酸乙酯 **（前体16）**		MS 284.09 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6):δ 8.30 (s, 1H), 6.96 (s, 1H), 4.13 (m, 2H), 4.05 (m, 2H), 3.15-3.22 (m, 2H), 1.97-2.01 (m, 2H), 1.37-1.47 (m, 2H) 和 1.15-1.21 (m, 6H).
1-(2-氯-4-吡啶基)哌啶-4-羧酸乙酯 **（前体17）**		MS $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6):δ 7.92 (d, *J*= 5.60 Hz, 1H), 6.82-6.84 (m, 2H), 4.07 (q, *J*= 7.20 Hz, 2H), 3.85-3.89 (m, 2H), 2.96-3.02 (m, 2H), 2.60-2.66 (m, 1H), 1.84-1.87 (m, 2H), 1.48-1.57 (m, 2H) 和 1.17 (t, *J*= 7.20 Hz, 3H).
2-氯-N-(2-吗啉基乙基)嘧啶-4-胺 **（前体18）**		MS 243.11 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6):δ 7.87(m, 2H), 6.48 (d, *J*= 5.60 Hz, 1H), 3.57 (m, 4H), 3.39 (m, 2H), 2.45 (m, 6H),
2-氯-N-(2-甲氧基乙基)嘧啶-4-胺 **（前体19）**		MS 188.01 $[M+H]^+$. ^{1}H NMR **($CDCl_3$,400 MHz)**:δ 7.99 (d, *J*= 5.60 Hz, 1H), 6.26 (d, *J*= 5.60 Hz, 1H), 5.47 (br s, 1H), 3.55 (br s, 4H) 和 3.37 (s, 3H).
1-(2-氯嘧啶-4-基)氮杂环丁烷-3-醇 **（前体20）**		MS 185.98 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6):δ8.04 (d, *J*= 6.0 Hz, 1H), 6.37 (d, *J*= 6.0 Hz, 1H), 5.86 (m, 1H), 4.60 (m, 1H), 4.27 (m, 2H) 和 3.79 (m, 2H).
2-氯-4-(3-甲氧基氮杂环丁烷-1-基)嘧啶 **（前体21）**		MS 200.04 $[M+H]^+$. ^{1}H NMR **($CDCl_3$,400 MHz)**:δ 8.00 (d, *J*= 4.80 Hz, 1H), 6.08 (d, *J*= 6.0 Hz, 1H), 4.28-4.36 (m, 3H), 4.0 (m, 2H) 和 3.33 (s, 3H).
1-(2-氯嘧啶-4-基)-3-甲基-氮杂环丁烷-3-醇		MS 200.06 $[M+H]^+$. ^{1}H NMR **($CDCl_3$,400 MHz)**:δ 7.96 (d, *J*= 5.20 Hz, 1H), 6.05 (d, *J*= 5.60 Hz, 1H), 4.04 (br s, 4H) 和 1.61

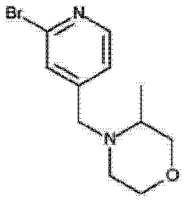
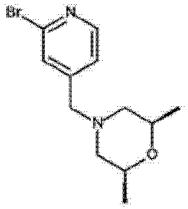
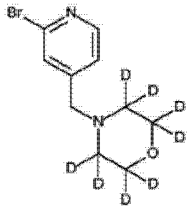
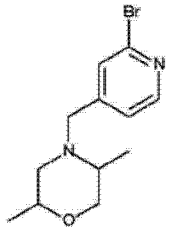
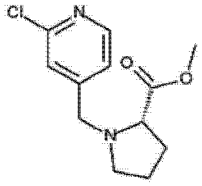
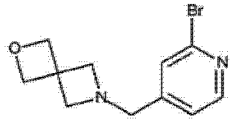
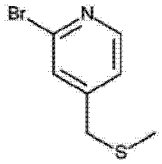
[0623]

（前体22）		(s, 3H).
4-(2-氯嘧啶-4-基)吗啉 （前体23）		MS 200.06 $[M+H]^+$. ^{1}H NMR **($CDCl_3$,400 MHz):**δ 8.08 (d, *J*= 6.0 Hz, 1H), 6.39 (d, *J*= 6.0 Hz, 1H), 3.78 (m, 4H) 和 3.64 (m, 4H).
2-氯-4-(4-乙基哌嗪-1-基)嘧啶 （前体24）		^{1}H NMR **($CDCl_3$,400 MHz):**δ 8.02 (d, *J*= 6.0 Hz, 1H), 6.38 (d, *J*= 5.60 Hz, 1H), 3.67 (m, 4H), 2.52 (m, 4H), 2.48 (q, *J*= 7.20 Hz, 2H) 和 1.12 (t, *J*= 7.20 Hz, 3H).
2-氯-4-[4-(2-甲氧基乙基)哌嗪-1-基]嘧啶 （前体25）		^{1}H NMR **($CDCl_3$,400 MHz):**δ 8.03 (d, *J*= 6.40 Hz, 1H), 6.38 (d, *J*= 6.0 Hz, 1H), 3.7 (m, 4H), 3.60 (t, *J*= 5.20 Hz, 2H), 3.29 (s, 3H), 2.64 (t, *J*= 5.20 Hz, 2H) 和 2.60 (m, 4H).
4-(2-氯-5-氟-嘧啶-4-基)吗啉 （前体26）		MS 218.0 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.95 (d, J= 6.0 Hz, 1H) 和 3.74-3.81 (m, 8H).
4-[(2-氯-4-吡啶基)氨基]-1-甲基-环己烷羧酸乙酯 （前体27）		MS 297.07 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6):δ 7.76 (d, *J*= 5.60 Hz, 1H), 6.75 (d, *J*= 8.0 Hz, 1H), 6.45 (m, 2H), 4.11 (q, *J*= 7.20 Hz, 2H), 2.50 (m, 1H), 2.06-2.08 (m, 2H), 1.78-1.81 (m, 2H), 1.29-1.36 (m, 4H), 1.21 (t, *J*= 7.20 Hz, 3H) 和 1.19 (s, 3H).
1-[(2-溴-4-吡啶基)甲基]-3-甲基-吡咯烷-3-醇 （前体28）		MS 271.97 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6):δ 8.29-8.31 (d, *J*= 4.80 Hz, 1H),7.57 (s, 1H),7.37-7.38 (d, *J*= 4.40 Hz, 1H), 4.58 (s, 1H), 3.64 (s, 2H), 2.64-2.68 (m, 2H), 2.42-2.44 (m, 2H), 1.72-1.75 (m, 2H) 和 1.23 (s, 3H).
1-[(2-溴-4-吡啶基)甲		^{1}H NMR (400 MHz, DMSO-d_6):δ

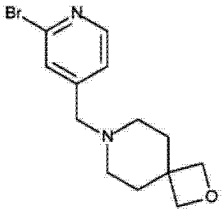
[0624]

基]-3-甲基-氮杂环丁烷-3-醇 **（前体29）**		8.29 (d, J= 5.20 Hz, 1H),7.50 (s, 1H),7.32 (d, *J*= 4.8 Hz, 1H), 5.21 (s, 1H), 3.61 (s, 2H), 3.33 (s, 2H), 2.90 (d, J= 6.40 Hz, 2H) 和 1.36 (s, 3H).
1-[(2-溴-4-吡啶基)甲基]氮杂环丁烷-3-醇 **（前体30）**		MS 243.07 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6):δ 8.28 (d, *J*= 4.80 Hz, 1H),7.50 (s, 1H),7.31 (d, *J*= 5.20 Hz, 1H), 5.35 (d, 1H), 4.17-4.25 (m, 1H), 3.59 (s, 2H), 3.48-3.54 (m, 2H) 和 2.77-2.81 (t, *J*= 6.80 Hz, 2H).
2-溴-4-[(3,3-二氟吡咯烷-1-基)甲基]吡啶 **（前体 31）**		MS 277.07 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6):δ 8.34 (d, *J*= 5.20 Hz, 1H),7.57 (s, 1H),7.39 (d, *J*= 5.20 Hz, 1H), 3.67 (s, 2H), 2.90 (m, 2H), 2.72 (m, 2H) 和 2.27 (m, 2H).
(3R)-1-[(2-溴-4-吡啶基)甲基]吡咯烷-3-醇 **（前体 32）**		MS 257.05 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6):δ 8.30 (d, J= 5.20 Hz, 1H), 7.56 (s, 1H), 7.37 (d, J= 4.80 Hz, 1H), 5.75 (s, 1H), 4.72 (d, J= 4.40 Hz, 1H), 3.55-3.65 (m, 2H), 2.61-2.68 (m, 2H), and 2.38-2.50 (m, 1H), 2.31-2.38 (m, 1H), 1.95-2.04 (m, 1H) 和 1.52-1.59 (m, 1H).
4-[(6-氯-3-吡啶基)甲基]吗啉 **（前体 33）**		MS 213.04 $[M+H]^+$.
N-[(2-溴-4-吡啶基)甲基]环丙胺 **（前体 34）**		MS 227.05 $[M+H]^+$.

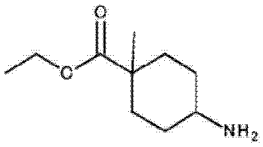
[0625]

4-[(2-溴-4-吡啶基)甲基]-3-甲基-吗啉 **（前体 35）**		MS 271.10 $[M+H]^+$.
(2R,6S)-4-[(2-溴-4-吡啶基)甲基]-2,6-二甲基-吗啉 **（前体 36）**		MS 285.07 $[M+H]^+$.
4-[(2-溴-4-吡啶基)甲基]-2,2,3,3,5,5,6,6-八氘-吗啉 **（前体 37）**		MS 265.17 $[M+H]^+$.
4-[(2-溴-4-吡啶基)甲基]-2,5-二甲基-吗啉 **（前体 38）**		MS 285.12 $[M+H]^+$.
(2S)-1-[(2-氯-4-吡啶基)甲基]吡咯烷-2-羧酸甲酯 **（前体 39）**		MS 255.06 $[M+H]^+$.
2-[(2-溴-4-吡啶基)甲基]-6-氧杂-2-氮杂螺[3.3]庚烷 **（前体 40）**		MS 269.07 $[M+H]^+$.
2-溴-4-(甲基硫烷基甲基)吡啶 **（前体 41）**		MS 220.0 $[M+H]^+$.

[0626]

7-[(2-溴-4-吡啶基)甲基]-2-氧杂-7-氮杂螺[3.5]壬烷 （前体 42）		MS 297.16 $[M+H]^+$.

[0627]

4-氨基-1-甲基环己烷羧酸乙酯 （前体 43）		MS 186.20 $[M+H]^+$.

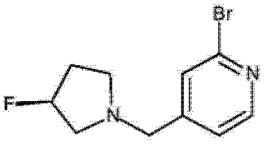
[0628] 4-氨基环己烷羧酸乙酯（i）：向冰冷的 4-氨基环己烷羧酸（5.0g,34.92mmol）的 EtOH(20mL) 溶液中加入亚硫酰氯（7.60mL,104.76mmol）。将混合物在 80℃加热 3h。真空蒸发溶剂以获得 i(7.23g)。^{1}H NMR(400MHz,DMSO-d_6)：δ 4.19(q,J = 7.20Hz,2H),3.71(m,1H),2.71(m,1H),2.06(m,2H),1.90(m,2H),1.69(m,2H),1.55(m,2H), 和 1.25(t,J = 7.20Hz,3H)。

[0629] 4-(1,3-二氧代异吲哚啉-2-基）环己烷羧酸乙酯（ii）：向 i(0.50g,2.92mmol) 的甲苯（10mL）溶液中加入 Et_3N(1.02mL,7.30mmol) 和邻苯二甲酸酐（0.56g,3.80mmol)。使用迪安斯塔克（dean-stark）设备将混合物回流 8h 以除去水。真空蒸发溶剂，加入水（50mL）并将混合物室温搅拌 30min。通过过滤收集如此得到的固体材料，并干燥以获得 ii(0.30g,34％)。^{1}H NMR(400MHz,DMSO-d_6)：δ 7.84(s,4H),4.19(q,J = 7.20Hz,2H),3.71(m,1H),2.71(m,1H),2.06(m,2H),1.90(m,2H),1.69(m,2H),1.60(m,2H), 和 1.23(t,J = 7.20Hz,3H)。

[0630] 4-(1,3-二氧代异吲哚啉-2-基)-1-甲基环己烷羧酸乙酯（iii）：将 ii(0.30g,1.0mmol) 的 THF(10mL) 溶液冷却到 -78℃，然后在 -78℃下逐滴加入 LDA(THF 中 1.60M,1.88mL,3.0mmol)。将混合物在 -78℃下搅拌 30min，随后在 -78℃下加入甲基碘 (0.311mL,5.0mmol)。将反应的温度缓慢提高至室温，并搅拌过夜。将反应冷却至 0℃，逐滴加入饱和 NH_4Cl 溶液（30mL）终止反应。使用 EtOAc(3x50mL) 萃取反应。合并的有机物用盐水洗涤、干燥（Na_2SO_4)、过滤并真空浓缩以获得 iii(0.30g,97％)。MS316.12$[M+H]^+$。

[0631] 4-氨基-1-甲基环己烷羧酸乙酯（前体 43）：向冰冷的 iii(0.30g,0.95mmol) 的 EtOH(20mL) 溶液中加入水合肼（0.115mL,2.38mmol)，并将所得反应混合物在 80℃加热 3h。真空蒸发溶剂，加入水（20mL）并使用 EtOAc(3x50mL) 萃取。有机物用盐水洗涤、干燥 (Na_2SO_4)、过滤并真空浓缩以获得前体 43(0.18g)。

[0632]

(S)-2-溴-4-((3-氟吡咯烷-1-基)甲基)吡啶（前体 44）		^{1}H NMR (DMSO-d_6,400 MHz):δ 8.29 (d, *J*= 4.8 Hz, 1H),7.50 (s, 1H),7.24-7.26 (d, *J*= 4.8, 1H), 5.12-5.25 (m, 1H), 3.65 (s, 2H) 和 2.70-2.91 (m, 3H), 2.45-2.51 (m, 1H), 和 2.03-2.25 (m, 2H).MS 259.05 $[M+H]^+$.

[0633] (2-溴吡啶-4-基)甲醇(i):在0℃和惰性气氛条件下,向2-溴吡啶-4-e醛(20g,107.52mmol)的MeOH(150mL)溶液中逐份加入硼氢化钠(12.0g,322.56mmol)。将混合物室温搅拌1h。加入饱和的NH_4Cl溶液,随后使用EtOAc(3x200mL)萃取。对合并的有机层进行干燥(Na_2SO_4)并真空蒸发以获得i(18.0g,90%)。^{1}H NMR(DMSO-d_6,400MHz):δ8.30(d,J = 4.8Hz,1H),7.54(s,1H),7.35(d,J = 4.8Hz,1H),5.55(t,J = 6.0Hz,1H)和4.53-4.54(d,J = 5.6Hz,2H)。2-溴-4-(溴甲基)吡啶(ii):在0℃和惰性气氛条件下向i(18g,95.74mmol)的甲苯(180mL)溶液中逐滴加入三溴化磷(13.4mL,143.62mmol)。将混合物100℃加热30min。使反应冷却至0℃并加入$NaHCO_3$溶液,随后用EtOAc(2x500mL)萃取。对合并的有机层进行干燥(Na_2SO_4)并真空蒸发。在二氧化硅上纯化残留物并使用15%EtOAc:己烷洗脱以获得ii(12.0g,50%)。^{1}H NMR($CDCl_3$,400MHz):δ8.35(d,J = 4.8Hz,1H),7.51(s,1H),7.26(d,J = 6.0Hz,1H)和4.34(s,2H)。MS251.80$[M+H]^+$。

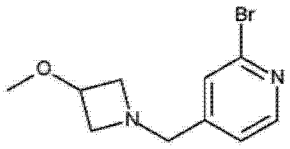
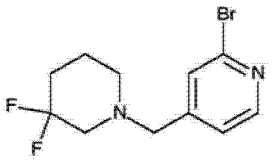
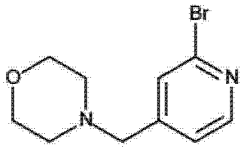
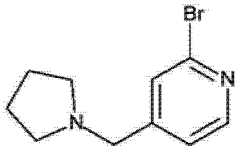
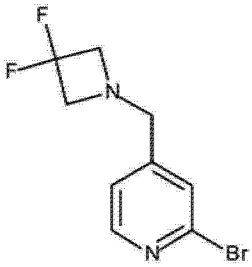
[0634] (S)-2-溴-4-((3-氟吡咯烷-1-基)甲基)吡啶(前体44):在惰性气氛条件下e,向冰冷的ii(3.0g,11.95mmol)的DMSO(10mL)溶液中加入KOH(1.0g,17.92mmol),随后加入(S)-3-氟吡咯烷盐酸盐(2.2g,17.92mmol)。将混合物在0℃下搅拌至室温,持续20min。使用冰水稀释混合物,随后使用EtOAc(3x150mL)萃取。合并的有机层用盐水洗涤,干燥(Na_2SO_4)并真空蒸发以获得前体44(3.0g,96%)。

[0635] 使用类似方法制备以下前体。

[0636]

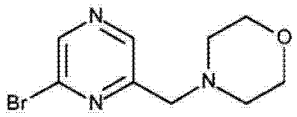
2-溴-4-[(3-甲氧		MS 257.19 $[M+H]^+$.^{1}H NMR (DMSO-d_6,400 MHz):δ 8.29 (d, *J*= 4.8

[0637]

基氮杂环丁烷-1-基)甲基]吡啶 **（前体 45）**		Hz, 1H),7.50 (s, 1H),7.32 (d, *J*= 4.8 Hz, 1H), 3.95-4.01 (m, 1H), 3.61 (s, 2H), 3.49-3.52 (m, 2H), 3.14 (s, 3H), 和 2.86-2.90 (m, 2H).
2-溴-4-[(3,3-二氟-1-哌啶基)甲基]吡啶 **（前体 46）**		MS 291.02 $[M+H]^+$.^{1}H NMR (DMSO-d_6,400 MHz):δ 8.34 (d, *J*= 4.80 Hz, 1H), 7.56 (s, 1H), 7.38 (d, *J*= 4.80 Hz, 1H), 3.62 (s, 2H), 2.65 (m, 2H), 2.40 (m, 2H), 1.84-1.90 (m, 2H) 和 1.63-1.67 (m, 2H).
4-[(2-溴-4-吡啶基)甲基]吗啉 **（前体 47）**		MS 257.49 $[M+H]^+$.^{1}H NMR (DMSO-d_6,400 MHz):δ 8.26 (d, *J*= 5.2 Hz, 1H),7.48 (s, 1H),7.22 (d, *J*= 4.80 Hz, 1H), 3.69-3.71 (t, *J*= 4.80 Hz, 4H), 3.45 (s, 2H) 和 2.41-2.43 (t, *J*= 4.40 Hz, 4H).
2-溴-4-(吡咯烷-1-基甲基)吡啶 **（前体48）**		^{1}H NMR (DMSO-d_6,400 MHz):δ 8.30 (d, *J*= 4.80 Hz, 1H), 7.55 (s, 1H), 7.37 (d, *J*= 4.80 Hz, 1H), 3.61 (s, 2H), 2.44 (m, 4H) 和1.70 (m, 4H).
2-溴-4-[(3,3-二氟氮杂环丁烷-1-基)甲基]吡啶 **（前体49）**		^{1}H NMR ($CDCl_3$, 400 MHz):δ 8.32 (d, *J*= 4.80 Hz, 1H), 7.47 (s, 1H), 7.25 (d, *J*= 4.80 Hz, 1H), 3.52 (s, 2H) 和 3.66 (m, 4H).

[0638] 向冰冷的 2- 溴异烟醛 (0.40g,2.15mmol) 的 THF(5mL) 溶液中加入 3,3- 二氟氮杂环丁烷盐酸盐 (0.41g,3.12mmol) 和 N- 甲基吗啉（催化）。反应在 0℃搅拌 15min，随后逐份加入氰基硼氢化钠 (0.41g,6.45mmol)。将混合物室温搅拌 16h。加入水 (50mL)，随后使用 EtOAc(3x100mL) 萃取。合并的有机物用盐水洗涤、干燥 (Na_2SO_4)、过滤并真空浓缩。在二氧化硅上通过色谱纯化 (30% EtOAc- 己烷）以得到前体 49(0.18g,32%）。

[0639]

4-((6-溴吡嗪-2-基)甲基)吗啉 **（前体 50）**		^{1}H-NMR (400 MHz, DMSO-d_6):δ 8.76 (s, 1H), 8.70 (s, 1H), 3.64 (s, 2H), 3.58 (br s, 4H) 和 2.43 (br s,

[0640]

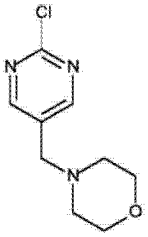
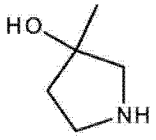
		4H).MS 258.0 $[M+H]^+$.

[0641] 2-溴-6-(溴甲基)吡嗪(i):室温下,向2-溴-6-甲基-吡嗪(3.0g,17.31mmol)的CCl_4(25mL)溶液中加入NBS(4.60g,26.01mmol)和AIBN(0.248g,1.734mmol)。将混合物在55℃下搅拌48h。加入水,随后使用EtOAc(3x100mL)萃取。合并的有机物用盐水洗涤、干燥(Na_2SO_4)并真空浓缩。在二氧化硅上纯化残留物并使用5% EtOAc:己烷洗脱以获得i(1.40g,32%)。^{1}H NMR($CDCl_3$,400MHz):δ 8.64(s,1H),8.62(s,1H)和4.50(s,2H)。

[0642] 4-((6-溴吡嗪-2-基)甲基)吗啉(前体50):向冰冷的i(1.29g,4.81mmol)的ACN(30mL)溶液中加入吗啉(0.46g,5.28mmol)并将混合物在0℃下搅拌45min。加入水并用EtOAc(3x50mL)萃取混合物。合并的有机物用盐水洗涤、干燥(Na_2SO_4)并真空浓缩。在二氧化硅上纯化残留物,使用90% EtOAc-己烷洗脱以获得前体50(0.6g,50%)。

[0643] 使用类似方法制备以下前体。

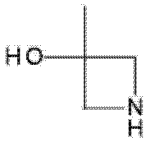
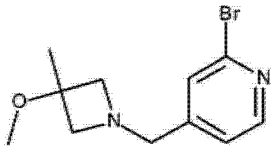
[0644]

4-[(2-氯嘧啶-5-基)甲基]吗啉 **(前体51)**		MS 214.10 $[M+H]^+$.^{1}H NMR ($CDCl_3$, 400 MHz):δ 8.61 (s, 2H), 3.72 (br s, 4H), 3.52 (s, 2H) 和 2.48 (br s, 4H).MS $[M+H]^+$.
3-甲基吡咯烷-3-醇盐酸盐 **(前体52)**		^{1}H-NMR (400 MHz, DMSO-d_6):δ 4.71 (s, 1H), 3.33-3.46 (m, 2H), 1.72-1.74 (m, 2H) 和 1.41 (s, 2H), 1.38 (s, 9H) 和 1.28 (s, 3H).MS 202.28 $[M+H]^+$.

[0645] 3-羟基-3-甲基吡咯烷-1-羧酸叔丁基酯(i):在惰性气氛下,向冰冷的3-氧代吡咯烷-1-羧酸叔丁基酯(1.0g,5.40mmol)的Et_2O(20mL)溶液中逐滴加入溴化甲基镁(3.50mL,10.80mmoL)。将混合物室温搅拌1h,然后使用饱和的NH_4Cl溶液终止反应,随后使用EtOAc(3x100mL)萃取。合并的有机层用盐水洗涤、干燥(Na_2SO_4)、过滤并真空浓缩。使用正戊烷研磨以获得i(1.0g,92%)。3-甲基吡咯烷-3-醇盐酸盐(前体52):0℃下向4M HCl的1,4-二噁烷(10mL)溶液中加入i(0.850g,4.22mmol)并将混合物室温搅拌2h。真空除去溶剂并使用Et_2O研磨以获得前体52(0.490g)。MS102.15$[M+H]^+$。

[0646] 使用类似方法制备以下前体。

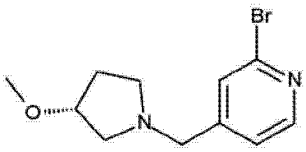
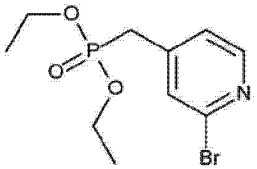
[0647]

3-甲基氮杂环丁烷-3-醇盐酸盐（前体 53）		^{1}H NMR (400 MHz, DMSO-d_6):δ 3.81-3.83 (m, 2H), 3.69-3.72 (m, 3H), 2.83 (br s, 1H) 和 1.42 (s, 3H).
2-溴-4-((3-甲氧基-3-甲基氮杂环丁烷-1-基)甲基)吡啶（前体 54）		MS 271.05 $[M+H]^+$.

[0648] 向冰冷的前体 29(0.75g,2.92mmol) 的 DMF(15mL) 溶液中逐份加入 NaH(矿物油中的 60％分散体,0.175g,4.38mmol)。将混合物在 0℃下搅拌 10min,随后逐滴加入甲基碘 (0.27mL,4.38mmol)。将反应混合物在 0℃下搅拌 30min。加入水 (10mL),随后使用 EtOAc(3x50mL) 萃取。合并的有机层用水、盐水洗涤、干燥 (Na_2SO_4) 并真空浓缩。在二氧化硅上纯化残留物,使用 40％ EtOAc: 己烷洗脱以获得前体 54(0.24g,30％)。

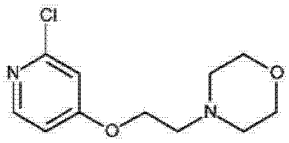
[0649] 使用类似方法制备以下前体。

[0650]

2-溴-4-[[(3R)-3-甲氧基吡咯烷-1-基]甲基]吡啶（前体 55）	 MS 271.0 $[M+H]^+$.
2-溴-4-(二乙氧基磷酰基甲基)吡啶（前体 56）	 MS 309.98 $[M+H]^+$.

[0651] 在密封的微波管中将 2- 溴 -4-(溴甲基) 吡啶 (2.3912mmol ;600mg) 和亚磷酸三乙酯 (2.6mmol ;440mg) 悬浮于 ACN(5mL) 中,并在微波炉中 100℃加热 1h。真空浓缩混合物以获得前体 56(700mg,95％)。

[0652]

4-(2-((2-氯吡啶-4-基)氧基)乙基)吗啉		^{1}H-NMR (400 MHz, DMSO-d_6):δ 8.18 (d, J= 6.0 Hz, 1H), 7.12 (d, J= 2.0 Hz, 1H),

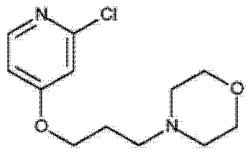
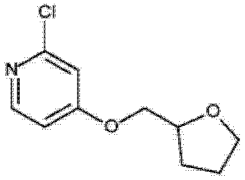
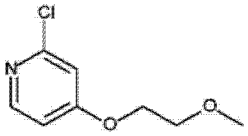
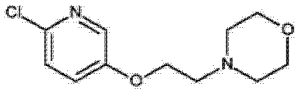
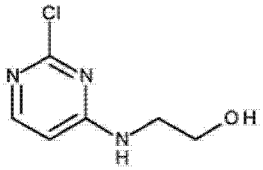
[0653]

（前体 57）		6.99-7.01 (m, 1H), 4.19-4.22 (t, J= 5.60 Hz, 2H), 3.55-3.57 (t, J= 4.80 Hz, 4H), 2.61 (t, J= 6.40 Hz, 2H) 和 2.45-2.50 (m, 4H).MS 243.09 $[M+H]^+$.

[0654] 向冰冷的 2- 氯吡啶 -4- 醇 (1.0g,7.72mmol) 和 4-(2- 氯乙基）吗啉盐酸盐 (1.16g,7.72mmol) 的 DMF(10mL) 溶液中加入 K_2CO_3(3.20g,23.16mmol)。将混合物室温搅拌 16h。加入水 (20mL)，随后使用 EtOAc(3x100mL) 萃取。合并的有机层用盐水洗涤、干燥 (Na_2SO_4) 并真空蒸发。在二氧化硅上纯化残留物并使用 5% MeOH:DCM 洗脱以获得前体 57(0.60g,33%)。

[0655] 使用类似方法制备以下前体。

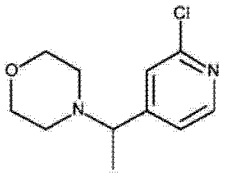
[0656]

4-[3-[(2-氯-4-吡啶基)氧基]丙基]吗啉 （前体 58）		1H-NMR (400 MHz, DMSO-d_6):δ 8.18 (d, J= 6.0 Hz, 1H), 7.10 (d, J= 2.0 Hz, 1H), 6.98-7.10 (dd, 分别 J= 2.0 Hz 和 5.60 Hz, 1H), 4.13 (t, J= 6.40 Hz, 2H), 3.55-3.57 (t, J= 4.80 Hz, 4H), 2.34-2.40 (m, 6H) 和 1.83-1.90 (m, 2H).
2-氯-4-(四氢呋喃-2-基甲氧基)吡啶 （前体 59）		MS 214.08 $[M+H]^+$.
2-氯-4-(2-甲氧基乙氧基)吡啶 （前体 60）		1H NMR ($CDCl_3$, 400 MHz):δ 8.18 (d, J= 5.60 Hz,1H), 6.88 (s, 1H), 6.79 (d, J= 5.60 Hz, 1H), 4.17 (m, 2H), 3.76 (m, 2H) 和 3.43 (s, 3H).
4-[2-[(6-氯-3-吡啶基)氧基]乙基]吗啉 （前体 61）		MS 243.11 $[M+H]^+$.
2-((2-氯嘧啶-4-基)氨基)乙醇： （前体 62）		^{1}H-NMR (400 MHz, DMSO-d_6):δ7.96 (br s, 1H), 7.87 (d, J= 5.60 Hz, 1H), 6.48 (d, J= 5.60 Hz, 1H), 4.81 (m, 1H) 和 3.52 (m, 4H).MS 174.01 $[M+H]^+$.

[0657] 将 2- 氯 -N-(2- 甲氧基乙基）嘧啶 -4- 胺 (1.0g,5.34mmol) 的 DCM(10mL) 溶液冷

却至 -10℃，随后逐滴加入 BBr_3(0.70mL,8.02mmol)。将混合物室温搅拌 3h。加入 $NaHCO_3$ 溶液 (5mL)，随后使用 DCM(2x50mL) 萃取。合并的有机物用水、盐水洗涤、干燥 (Na_2SO_4) 并真空蒸发。在二氧化硅上纯化残留物并使用 80% EtOAc: 己烷洗脱以获得白色固体状的前体 62(0.35g,38%)。

[0658]

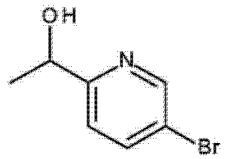
4-(1-(2-氯吡啶-4-基)乙基)吗啉（前体 63）		^{1}H-NMR (400 MHz, DMSO-d_6):δ 8.36 (d, J= 5.20 Hz, 1H), 7.44 (s, 1H), 7.37 (d, J= 4.80 Hz, 1H), 3.55 (m, 4H), 3.47 (q, J= 6.80 Hz, 1H), 2.24-2.39 (m, 4H) 和 1.27 (d, J= 6.80 Hz, 3H).

[0659] 1-(2-氯吡啶-4-基)乙醇 (i)：向冰冷的 1-(2-氯-4-吡啶基)乙酮 (1.0g,6.42mmol) 的 MeOH 溶液中加入 $NaBH_4$(0.73g,19.21mmol) 并将溶液室温搅拌 30min。随后使用饱和的 NH_4Cl 溶液终止反应，随后用 EtOAc(3x100mL) 萃取。合并的有机层用盐水洗涤、干燥 (Na_2SO_4) 并真空蒸发以获得 i(0.61g,60%)。MS158.10$[M+H]^+$。

[0660] 1-(2-氯吡啶-4-基)乙基甲磺酸酯 (ii)：向冰冷的 i(0.25g,1.58mmol) 的 DCM(10mL) 溶液中加入 Et_3N(0.43mL,3.16mmol)，并将所得溶液在相同温度下搅拌 15min，随后加入甲磺酰氯 (0.18mL,2.37mmol)。将混合物室温搅拌 4h。加入水终止反应并使用 EtOAc(3x100mL) 萃取。合并的有机层用盐水洗涤、干燥 (Na_2SO_4) 并真空蒸发以获得 ii(0.30g,80%)。MS236.38$[M+H]^+$。

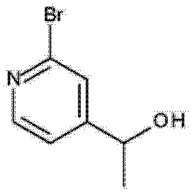
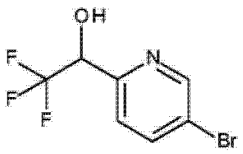
[0661] 4-(1-(2-氯吡啶-4-基)乙基)吗啉（前体 63）：向冰冷的 ii(0.30g,1.33mmol) 的 DMSO(5mL) 溶液中加入粉末状的 KOH(0.11g,1.99mmol)。将混合物在 0℃下搅拌 15min，随后加入吗啉 (0.23g,2.66mmol) 并室温搅拌混合物 16h。向反应物中加入冰水，随后使用 EtOAc(3x100mL) 萃取。合并的有机层用盐水洗涤、干燥 (Na_2SO_4) 并真空蒸发以获得前体 63(0.28g,93%)。

[0662]

1-(5-溴吡啶-2-基)乙醇（前体 64）		^{1}H NMR (DMSO-d_6,400 MHz):δ 8.59 (m, 1H), 8.03 (d, J= 8.40 Hz, 1H), 7.49 (d, J= 8.40 Hz, 1H), 5.50 (d, J= 4.40 Hz, 1H), 4.69 (m, 1H), 1.34 (d, J= 6.40 Hz, 3H).

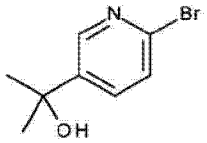
[0663] 向冰冷的 5-溴吡啶-2-醛 (1.0g,5.37mmol) 的 THF(10.0mL) 溶液中加入甲基溴化镁 (3.44mL,6.88mmol,2M 在 Et_2O 中)。将所得反应混合物室温搅拌 16h。加入水 (100mL)，随后使用 EtOAc(3x100mL) 萃取。合并的有机物用盐水洗涤、干燥 (Na_2SO_4)、过滤并真空浓缩。在二氧化硅上纯化残留物 (50% EtOAc-己烷) 以获得前体 64(0.80g,74%)。使用类似方法制备以下前体。

[0664]

1-(2-溴-4-吡啶基)乙醇（前体 65）		MS 202 $[M+H]^+$.
1-(5-溴吡啶-2-基)-2,2,2-三氟乙醇（前体 66）		^{1}H NMR (DMSO-d_6,400 MHz):δ 8.73 (m, 1H), 8.17 (dd, *J*= 2.0 and 8.40 Hz, 1H), 7.60 (d, *J*= 8.40 Hz, 1H), 7.16 (d, *J*= 6.0 Hz, 1H) 和5.15 (m, 1H).MS 255.88 $[M+H]^+$.

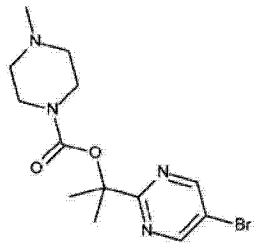
[0665] 向 5-溴吡啶-2-醛(0.5g,2.69mmol)的 THF(10mL)冰冷溶液中加入三甲基(三氟甲基)硅烷(0.57g,4.03mmol),随后加入 TBAF(6.73mL,6.73mmol,1.0M THF)。将混合物室温搅拌 16h。加入水(100mL),随后使用 EtOAc(3x50mL)萃取。合并的有机物用盐水洗涤、干燥(Na_2SO_4)、过滤并真空浓缩。在二氧化硅上纯化残留物(20% EtOAc-己烷)以获得前体 66(0.61g,89%)。

[0666]

2-(6-溴-3-吡啶基)丙-2-醇（前体 67）	 MS 216 $[M+H]^+$.

[0667] 0℃下,向 1-(6-溴-3-吡啶基)乙酮(500mg,2.68mmol)的 THF(20mL)溶液中逐滴加入甲基溴化镁(3M 在二乙醚中,1.2mL,3.7mmol)并使混合物升温至室温并搅拌 60min。将混合物重新冷却至 0℃,并加入 $NaHCO_3$ 溶液(100mL)。混合物用 EtOAc(100mL)萃取。分离有机层并用另一部分 EtOAc(100mL)来萃取水层。合并有机层、干燥($MgSO_4$)并真空浓缩。通过色谱纯化,在二氧化硅上使用含 0-5%甲醇的 DCM 洗脱,随后进一步色谱,在二氧化硅上使用含 0-50% EtOAc 的正庚烷洗脱以获得前体 67。

[0668]

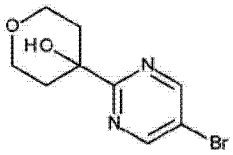
2-(5-溴嘧啶-2-基)丙-2-基 4-甲基哌嗪-1-羧酸酯（前体68）	 MS 344.87和342.87 $[M+H]^+$.

[0669] 2-(5-溴嘧啶-2-基)丙-2-基 4-硝基苯基碳酸酯(i):0℃下,向前体 1 的 THF(10ml)溶液中加入氢化钠(110mg,2.8mmol)并搅拌 1h。向该混合物中逐份加入 4-硝基苯基氯代甲酸酯(560mg,2.8mmol)并将溶液在 0℃下搅拌 1h。加入 EtOAc(3ml)和水,分

离有机层，干燥并浓缩以获得 i(900mg)。

[0670] 2-(5-溴嘧啶-2-基)丙-2-基4-甲基哌嗪-1-羧酸酯(前体68)：向 i(1g,2.1mmol)的DMF(10mL)溶液中加入1-甲基哌嗪(1.05g,10.47mmol)并室温搅拌18h。真空浓缩混合物使得残留物在EtOAc(20mL)和水(10mL)之间分配，分离有机层并使用水(2x5mL)洗涤、干燥($MgSO_4$)、过滤并真空浓缩。在二氧化硅上通过色谱纯化，使用0-10%MeOH/DCM洗脱以得到前体68(144mg,20%)。

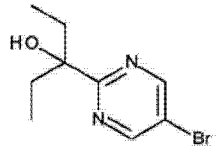
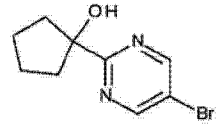
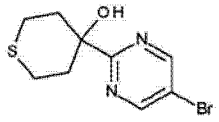
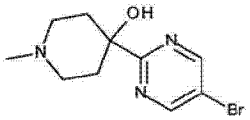
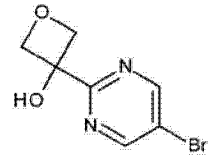
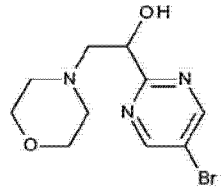
[0671]

4-(5-溴嘧啶-2-基)四氢-2*H*-吡喃-4-醇 **(前体69)**	 MS 258.92 和 260.88 $[M+H]^+$.

[0672] -78℃下，向n-BuLi(2.76mL1.52M)的甲苯(8mL)溶液中逐滴加入5-溴-2-碘-嘧啶(1.14g,4mmol)的甲苯(4mL)溶液。78℃下搅拌1h后，将已在**3Å**分子筛上干燥了>30min的四氢-4H-吡喃-4-酮(1.6g,1.5mL,16mmol)一次性加入并剧烈搅拌。使反应升至室温并搅拌3h。使用NH_4Cl(10mL)终止反应并使用EtOAc(4x20mL)萃取。合并有机层、干燥(Na_2SO_4)、真空浓缩。通过快速色谱(庚烷中10%-45%EtOAc)纯化残留物以得到前体69(535mg,53%)。

[0673] 使用类似方法制备以下前体。

[0674]

3-(5-溴嘧啶-2-基)戊-3-醇 （前体 70）	 MS 244.86 $[M+H]^+$.
1-(5-溴嘧啶-2-基)环戊醇 （前体 71）	 MS 242.88 $[M+H]^+$.
4-(5-溴嘧啶-2-基)四氢噻喃-4-醇 （前体 72）	 MS 276.91 $[M+H]^+$.
4-(5-溴嘧啶-2-基)-1-甲基-哌啶-4-醇 （前体 73）	 MS 272.02 $[M+H]^+$.
3-(5-溴嘧啶-2-基)氧杂环丁烷-3-醇 （前体 74）	 MS 230.96和232.94 $[M+H]^+$.
1-(5-溴嘧啶-2-基)-2-吗啉基-乙醇 （前体 75）	 MS 288.05和290.01 $[M+H]^+$.

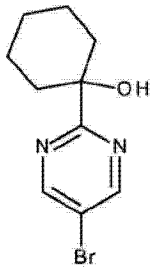
[0675] 5-溴-2-乙烯基-嘧啶(i)：将5-溴-2-碘-嘧啶(2.15g,7.55mmol)、4,4,5,5-四甲基-2-乙烯基-1,3,2-二氧杂环戊硼烷(1.60mL,9.43mmol)和$PdCl_2$(dppf).(300mg,0.40mmol)溶解在1,4-二噁烷(15mL)中。加入Cs_2CO_3(4.91g,15.1mmol)的水(5mL)溶液并将混合物在80℃加热30min。反应混合物用EtOAc(100mL)稀释,用水、盐水洗涤并且分离。干燥并真空浓缩有机部分。在二氧化硅上通过色谱纯化，使用5-25% EtOAc/庚烷洗脱以得到i(1.10g,79%)。MS 185.11和187.09$[M+H]^+$。

[0676] 5-溴-2-(环氧乙烷-2-基)嘧啶(ii)：将乙酸(680μL,11.9mmol)和i(1.1g,5.95mmol)溶解在1,4-二噁烷(30mL)和水(80mL)中。将溶液冷却至0℃并逐份加入NBS(1.27g,7.13mmol)。使反应升至室温,随后加入2M NaOH(50mL)并持续搅拌16h。

使用水稀释反应并使用 EtOAc 萃取。使用盐水清洗有机部分并进行干燥 (Na_2SO_4)。在二氧化硅上通过色谱纯化并使用 10-50% EtOAc/ 庚烷洗脱以得到 ii(140mg,12%)。MS200.92 和 202.91$[M+H]^+$。

[0677] 1-(5- 溴嘧啶 -2- 基)-2- 吗啉基 - 乙醇(前体 75):在微波辐射下,将 ii(140mg,0.70mmol) 的吗啉 (2.0mL) 溶液在 120℃加热 1h。在 N_2 气流下浓缩干燥即可得到前体 75。

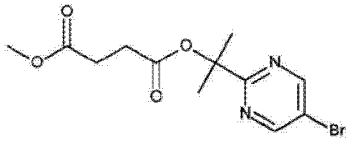
[0678]

1-(5-溴嘧啶-2-基)环己醇（前体76）	 MS 257.0和259.0; 1:1 $[M+H]^+$.

[0679] 将 5- 溴嘧啶 -2- 羧酸甲酯 (250mg ;1.15mmol) 溶解在无水 THF(10mL) 中并冷却至 0℃。逐滴加入五亚甲基二(溴化镁)(0.5M 在 THF 中,3.0mL,1.3mmol) 并将混合物搅拌 15min。使用 MeOH(0.5mL) 终止反应,使用 EtOAc(100mL) 分层,使用水 (100mL) 洗涤,干燥 ($MgSO_4$) 并真空浓缩。在二氧化硅上通过色谱纯化,使用含 0-100% EtOAc 的正庚烷洗脱以得到前体 76(7%)。

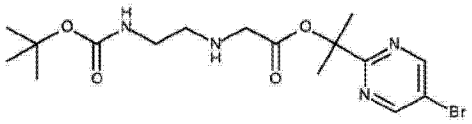
[0680] 应理解可如以下示例所示形成前述前体中任意一个的酯。

[0681]

*O*4-[1-(5-溴嘧啶-2-基)-1-甲基-乙基] O1-甲基丁二酸酯（前体 77）	 MS 330.79 和 332.83 $[M+H]^+$.

[0682] 在氩气下将前体 1(8.0g,36.9mmol) 溶解在无水 DMF(80mL) 中并在冰浴中冷却。逐份加入氢化钠 (1.62g,含 60%的矿物油,40.5mmol),反应搅拌 10min。加入 4- 氯 -4- 氧代丁酸甲酯 (13.6mL,111mmol) 并将混合物升至室温。18h 后加入更多的 4- 氯 -4- 氧代丁酸甲酯 (4.50mL,36.9mmol) 并持续搅拌。25.5h 后加入更多的 4- 氯 -4- 氧代丁酸甲酯 (4.50mL,36.9mmol) 并持续搅拌。45h 后使用水终止反应,随后在冰浴中冷却并使用 $NaHCO_3$(饱和水)溶液碱化至 pH9。混合物用 EtOAc(4x200mL) 萃取。合并的有机相用水和盐水洗涤,干燥 (Na_2SO_4) 并真空浓缩至干以形成油状物。通过色谱、Biotage SP4、120gSi 管、含 10-100% EtOAc 的环己烷纯化混合物以得到前体 77,8.02g(66%)。

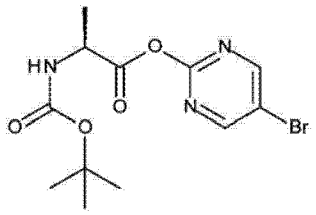
[0683]

[1-(5-溴嘧啶-2-基)-1-甲基-乙基] 2-[2-(叔丁氧基羰基氨基)乙基氨基]乙酸酯（**前体 78**）	 MS 292.69, 294.68 和 296.69 $[M+H]^+$.

[0684] [1-(5-溴嘧啶-2-基)-1-甲基-乙基]2-氯乙酸酯(i)：在氩气下将前体1(1.03g,4.75mmol)溶解在无水DMF(15mL)中。加入氢化钠(209mg,60%,矿物油中,5.22mmol)并将混合物搅拌15min。加入氯乙酰氯(1.13mL,14.2mmol)并在室温搅拌混合物。18h后,加入更多的氯乙酰氯(1.13mL,14.2mmol)并持续搅拌。42h后使用水终止反应并将混合物萃取至EtOAc(4x50mL)中。合并的有机相用水和盐水洗涤,干燥(Na_2SO_4)并真空浓缩至干。在二氧化硅上通过色谱纯化,使用含0-20%EtOAc的正庚烷洗脱以得到i(930mg,67%)。

[0685] [1-(5-溴嘧啶-2-基)-1-甲基-乙基]2-[2-(叔丁氧基羰基氨基)乙基氨基]乙酸酯(前体78)：在氩气下将DMAP(4mg,0.03mmol)和i(97mg,0.33mmol)溶解在无水THF(5mL)中,并加入DIPEA(0.09mL,0.50mmol)和N-Boc-乙二胺(0.06mL,0.40mmol)。将混合物在室温搅拌1h,随后升温至50℃持续17h。加入更多的DIPEA(0.09mL,0.50mmol)、DMAP(4mg,0.03mmol)和N-Boc-乙二胺(0.06mL,0.40mmol)并将温度升至60℃。30h后,将混合物冷却至室温,使用水终止并萃取至EtOAc(4x10mL)中。合并的有机相用盐水洗涤,干燥(Na_2SO_4)并真空浓缩至干以得到前体78(191mg)。MS416.97和418.95$[M+H]^+$。

[0686]

(5-溴嘧啶-2-基) (2S)-2-(叔丁氧基羰基氨基)丙酸酯（**前体 79**）	

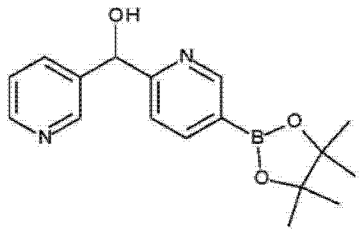
[0687]

	MS 387.82 和 389.81 $[M+H]^+$.

[0688] 将(2S)-2-(叔丁氧基羰基氨基)丙酸(95mg,0.50mmol)、前体1(109mg,0.50mmol)和DMAP(61mg,0.50mmol)溶解在THF(2mL)中。最后加入DCC(104mg,0.50mmol)并将反应在氩气下室温搅拌16h。加入额外的(2S)-2-(叔丁氧基羰基氨基)丙酸(95mg,0.50mmol)、DMAP(61mg,0.50mmol)和DCC(104mg,0.50mmol),并室温搅拌16h。将反应物过滤并用THF洗涤并真空浓缩滤液。在二氧化硅上通过色谱纯化,使用10-50%EtOAc/庚烷洗脱,随后在二氧化硅上通过色谱纯化,使用0-10%MeOH/DCM洗脱以得到前体79(148mg,76%)。

[0689] 应理解可如以下示例所示形成前述前体中任意一个的硼酸及其酯,例如硼酸酯(如4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基和5,5-二甲基-1,3,2-二氧杂环戊硼烷-2-基)。

[0690]

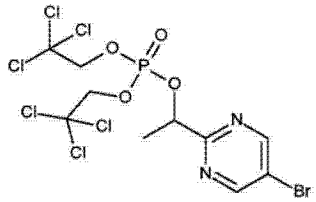
3-吡啶基-[5-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)-2-吡啶基]甲醇 （前体80）	 MS 313.18 $[M+H]^+$.

[0691] (5-溴吡啶-2-基)(吡啶-3-基)甲酮(i):将3-溴吡啶(2.50g,15.82mmol)的THF(25.0mL)溶液冷却至-78℃,随后逐滴加入n-BuLi(1.60M在己烷中,11.90mL,18.98mmol)。将混合物在-78℃下搅拌30min,随后在-78℃下加入溶解在最少量THF中的5-溴吡啶甲酸甲酯(4.10g,18.98mmol)。使反应的温度缓慢升至室温然后搅拌过夜。然后将反应冷却至0℃并加入饱和的NH_4Cl溶液(50mL),随后用EtOAc(3x100mL)萃取。合并的有机物用盐水洗涤、干燥(Na_2SO_4)、过滤并真空浓缩。在二氧化硅上纯化残留物,使用25%EtOAc-己烷洗脱以获得i(2.50g,60%)。MS263.09$[M+H]^+$。

[0692] (5-溴吡啶-2-基)(吡啶-3-基)甲醇(ii):向冰冷的i(2.50g,9.50mmol)的MeOH(25.0mL)溶液中逐份加入硼氢化钠(1.05g,28.50mmol)。将所得混合物室温搅拌30min。加入水(50mL),随后使用EtOAc(3x100mL)萃取。对合并的有机层干燥(Na_2SO_4)、过滤并真空蒸发以获得ii(1.75g,70%)。MS265.11$(M+H)^+$。

[0693] 3-吡啶基-[5-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)-2-吡啶基]甲醇(前体80):向ii(0.50g,1.89mmol)的1,4-二噁烷(10mL)溶液中加入双(频哪醇合)二硼(0.53g,2.08mmol)和KOAc(0.28g,2.84mmol)。通过吹扫$N_2$15min使e反应脱气,然后加入$Pd_2(dba)_3(0)$(0.10g,0.10mmol)和三环己基膦(0.06g,0.23mmol)。使反应脱气10min,然后加热到80℃持续2h。将所得混合物冷却到室温,并通过硅藻土床过滤。真空浓缩滤液以获得前体80(0.41g,70%)。

[0694]

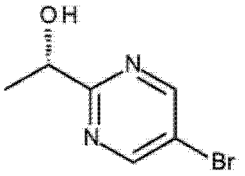
1-(5-溴嘧啶-2-基)乙基 二(2,2,2-三氯乙基)磷酸酯（前体81）	 MS:546.74 $[M+H]^+$。

[0695] 向二(2,2,2-三氯乙基)氯磷酸酯(450mg)和前体4(200mg)的THF(10mL)溶液中加入N,N-二甲基吡啶-4-胺(120mg),并将混合物在70℃下加热1h。将混合物冷却至室温并过滤。真空浓缩滤液并在二氧化硅上通过色谱纯化,使用40%EtOAc/正庚烷-80%EtOAc/正庚烷洗脱以得到前体81(300mg,56%)。

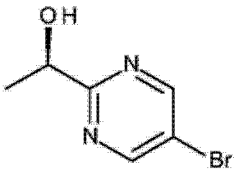
[0696] 应理解前述含有手性醇的前体中任意一个均可如以下示例所示由对映异构体拆解试剂合成和/或通过本领域技术人员已知的适当手性分离方法(如手性HPLC)分离成其各自的对映异构体。

[0697] (1S)-1-(5-溴嘧啶-2-基)乙醇(前体82)和(1R)-1-(5-溴嘧啶-2-基)乙醇(前体83)

[0698]



；和



。

[0699] ^{1}H NMR(400MHz,$CDCl_3$)：δ 8.78(s,2H)；4.92(dq,J = 5.6,6.8Hz,1H)；3.80(1H,d,J = 5.6Hz)；1.55(t,J = 6.8Hz,3H)。

[0700] 1-(5-溴嘧啶-2-基)乙基(2R)-2-(叔丁氧基羰基氨基)-3-甲基-丁酸酯(i)：将前体4(27.8g,137mmol)、Boc-D-缬氨酸(32.7g,151mmol)和DMAP(10.0g,82.2mmol)的混合物溶解在THF(200mL)中。将混合物在冰浴中冷却。加入DCC(31.1g,151mmol)的THF(50mL)溶液。10min后,移开冷却浴。将混合物搅拌过夜,过滤,使用EtOAc分几次洗涤DCU沉淀并浓缩合并的滤液。随后通过二氧化硅塞(20%EtOAc/庚烷)洗脱残留物,以得到i(64.7g)。

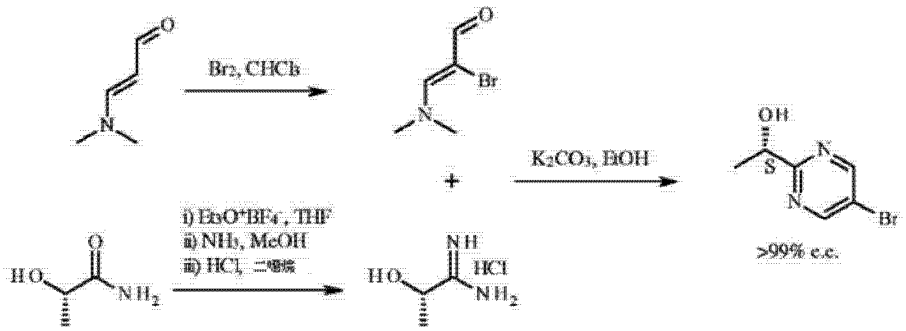
[0701] [(1S)-1-(5-溴嘧啶-2-基)乙基](2R)-2-(叔丁氧基羰基氨基)-3-甲基-丁酸酯(ii)：将i(64.7g)从热庚烷中结晶。通过过滤收集得到固体,并再从热庚烷中结晶以生成ii(15.4g)。

[0702] (1S)-1-(5-溴嘧啶-2-基)乙醇(前体82)：将Amberlite®碱性离子交换树脂和ii(15.4g,38.3mmol)在MeOH(50mL)中,在室温下搅拌过夜。使用1:1的MeOH/DCM,通过二氧化硅垫过滤悬浮液并真空浓缩滤液。从热庚烷中结晶以生成前体82(5.85g)。使用Boc-L-缬氨酸,用类似方法制备(1S)-1-(5-溴嘧啶-2-基)乙醇(前体83)。还可使用光延转换(mitsunobu inversion)将一种对映异构体变为所需的对映异构体。

[0703] 手性HPLC用于显示对映异构体的手性纯度(柱：Chirapak IC,0.46cm x25cm；20min等度梯度；5:95EtOH:正己烷+0.1%二乙胺)保留时间= 14.65min/17.53min。

[0704] 或者,可如下所示合成前体82(S-对映异构体)。

[0705]



[0706] (Z)-2-溴-3-(二甲基氨基)丙-2-烯醛：将3-(二甲基氨基)丙烯醛(25g)溶解在氯仿(250mL)中并在冰浴/水浴中冷却混合物。逐滴加入溴(40g；13mL)并在加样结束后立即使反应升至室温并搅拌1小时。使用DCM(150mL)稀释反应,并通过加入饱和的Na_2SO_5水溶液(50mL)和饱和的$NaHCO_3$水溶液(250mL)终止反应。收集有机层并干燥(MgSO4),并

真空除去溶剂。一旦材料固化后，即将其悬浮于乙酸乙酯：庚烷（1:1-100mL）中，并通过过滤收集得到的固体材料。使用乙酸乙酯：庚烷洗涤并空气干燥，以得到（Z)-2- 溴 -3-（二甲基氨基）丙 -2- 烯醛，一种黄褐色固体（25g，75％）。^{1}H NMR($CDCl_3$) δ 8.85(s,1H),7.2(s,1H),3.36(s,6H)。

[0707] (2S)-2- 羟基丙烷脒盐酸盐：将（2S)-2- 羟基丙烷酰胺（20g）置于装有 THF(100mL) 的烧瓶中，并加入三乙基氧鎓四氟硼酸盐（47g)，并将混合物搅拌 1 小时。除去溶剂并将残留物溶解在甲醇（100mL）中并在约 10min 内加入氨（7M，甲醇中）(150mL)，将反应混合物在冷水浴中冷却。添加完成后，立即使反应升至室温。将得到的悬浮液浓缩成稠和的混合物，用乙酸乙酯稀释并通过硅藻土过滤。将滤液冷却至约 10℃并逐滴加入 HCl(4M，二噁烷中)(100mL)。搅拌 90min 后，过滤混合物以收集白色沉淀（使用乙酸乙酯洗涤并随后在 40℃下在真空烘箱中干燥以获得白色固体状的（2S)-2- 羟基丙烷脒盐酸盐（12g，43％）。^{1}H NMR($CDCl_3$) δ 8.8(m,4H),6.26(s,1H),4.43(q,J = 6.7Hz,1H),1.35(d,J = 6.7Hz,3H)。

[0708] (1S)-1-(5- 溴嘧啶 -2- 基）乙醇：将（Z)-2- 溴 -3-（二甲基氨基）丙 -2- 烯醛（11.5g)、碳酸钾（13.4g)、乙醇（200mL）和 2- 羟基 -2- 甲基 - 丙烷脒盐酸盐（12.1g）置于烧瓶中，并将混合物在 85℃加热过夜。冷却反应混合物并过滤混合物，使用乙醇洗涤并使用二氧化硅凝胶真空浓缩合并的滤液。在二氧化硅上通过色谱纯化该残留物，使用含 0-50％乙酸乙酯的庚烷洗脱以获得白色固体状的（1S)-1-(5- 溴嘧啶 -2- 基）乙醇（2.1g，16％）。^{1}H NMR($CDCl_3$) δ 8.83(s,2H),4.98(m,1H),3.8(m,1H),1.6(d,J = 6.6Hz,3H)。手性 HPLC：柱：Chirapak IC，0.46cm x25cm；20min 等度梯度；5:95EtOH: 正己烷 +0.1％二乙胺，保留时间＝ 14.08min。（外消旋混合物：约 14.5min：S 异构体；约 17.5min：R 异构体）。

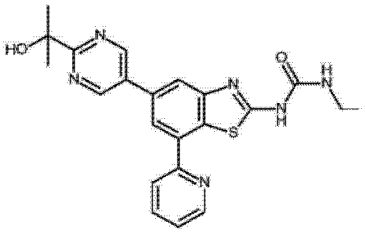
[0709] 可使用 R- 乳酰胺生成前体 83(R- 对映异构体）。

[0710] 一旦形成，即可将前体 82 或前体 83 偶联至中间体核，随后如果需要，任选地采用光延转换（mitsunobu inversion）条件以获得其他对映异构体形式。

[0711] 通用方法 A 的实施例

[0712] 1- 乙基 -3-(5-(2-(2- 羟基丙烷 -2- 基）嘧啶 -5- 基)-7-（吡啶 -2- 基）苯并 [d] 噻唑 -2- 基）脲（1)

[0713]



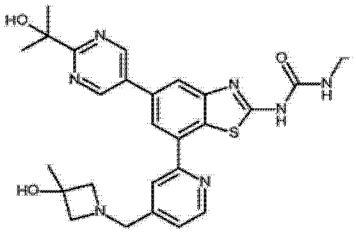
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 2H), 8.77 (d, J = 4.1 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.93 (t, J = 8.7 Hz, 1H), 7.91 - 7.77 (m, 2H), 7.35 - 7.29 (m, 1H), 3.44 - 3.31 (m, 3H), 1.66 (s, 6H), 1.32 - 1.15 (m, 4H).MS:435.1 $[M+H]^+$.

[0714] 将前体 1(50mg) 与中间体 1(100mg)、Cs_2CO_3(67mg)、Pd(dppf)Cl_2(16mg)、DMF(3mL) 和水（0.5mL）一起置于烧瓶中，并将混合物在 85℃加热 16h。将混合物冷却至室温，并在水（50mL）和 EtOAc(50mL) 之间分配。收集有机层，并用 EtOAc(2x50mL) 萃取水层。干燥 ($MgSO_4$) 合并的有机层并真空除去溶剂。在二氧化硅上通过色谱纯化，使用 DCM 中 0-10％梯度的 MeOH 洗脱以得到化合物 1(12mg)。

[0715] 使用类似方法制备以下化合物，注意可使用替代的催化剂、碱、溶剂和反应时间，且脲可能需要以 5- 甲基 -1,3,5- 三嗪 -2- 酮的形式保护。

[0716] 1-乙基-3-(7-(4-((3-羟基-3-甲基氮杂环丁烷-1-基)甲基)吡啶-2-基)-5-(2-(2-羟基丙烷-2-基)嘧啶-5-基)苯并[d]噻唑-2-基)脲(2)

[0717]



^{1}H NMR (DMSO-d_6):δ 10.61 (br s, 1H), 9.33 (s, 2H), 8.72 (d, J= 5.20 Hz, 1H), 8.34 (m, 2H), 8.12 (s, 1H), 7.36 (m, 1H), 6.84 (m, 1H), 5.21 (s, 1H), 5.15 (s, 1H), 3.74 (s, 2H), 3.17-3.26 (m, 4H), 2.97-2.99 (m, 2H), 1.57 (s, 6H), 1.38 (s, 3H) 和 1.09 (t, J=7.20 Hz, 3H).MS:534.32 $[M+H]^+$.

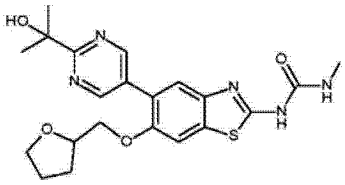
[0718] 1-(7-(5,5-二甲基-1,3,2-二氧杂硼杂己环(dioxaborinan)-2-基)-5-(2-(2-羟基丙烷-2-基)嘧啶-5-基)苯并[d]噻唑-2-基)-3-乙基-5-甲基-1,3,5-三嗪-2-酮(i):向中间体4(0.25g,0.51mmol)的甲苯(10mL)溶液中加入双(新戊基乙二醇)二硼(0.23g,1.01mmol)和乙酸钾(0.15g,1.53mmol)。将反应物通过N_2吹扫脱气15min,然后加入Pd(dppf)Cl_2(0.041g,0.091mmol)。将混合物脱气15min,然后在130℃加热30min。将混合物冷却至室温并通过硅藻土过滤。真空浓缩滤液以获得i(0.21g,80%粗)。MS:455.20$[M-H]^+$,(观察到相应硼酸的MS)。

[0719] 1-乙基-3-(7-(4-((3-羟基-3-甲基氮杂环丁烷-1-基)甲基)吡啶-2-基)-5-(2-(2-羟基丙烷-2-基)嘧啶-5-基)苯并[d]噻唑-2-基))-5-甲基-1,3,5-三嗪-2-酮(ii):向i(0.427g,0.81mmol)的1,4-二噁烷-水(9:1,10mL)溶液中加入前体29(0.231g,0.90mmol)和Cs_2CO_3(0.791g,2.43mmol)。将反应混合物通过N_2吹扫脱气15min,然后加入Pd(dppf)Cl_2(0.066g,0.08mmol)。将混合物在110℃的微波炉中加热30min。用水稀释混合物并用EtOAc(2x50mL)萃取。合并的有机物用盐水洗涤、干燥(Na_2SO_4)并真空浓缩。在二氧化硅上纯化残留物并使用7%MeOH:DCM洗脱以获得ii(0.303g,63%)。^{1}H-NMR(400MHz,DMSO-d6):δ9.34(s,2H),8.75(d,J=4.40Hz,1H),8.38(m,2H),8.20(s,1H),7.37(m,1H),5.23(br s,1H),5.15(s,3H),4.38(s,2H),3.75(br s,2H),3.38(m,2H),3.26(m,2H),2.94(m,2H),2.55(s,3H),1.57(s,6H),1.38(s,3H),和1.12(t,J=7.20Hz,3H)。MS:589.31$[M+H]^+$。

[0720] 1-乙基-3-(7-(4-((3-羟基-3-甲基氮杂环丁烷-1-基)甲基)吡啶-2-基)-5-(2-(2-羟基丙烷-2-基)嘧啶-5-基)苯并[d]噻唑-2-基)脲(2):用HCl(g)对ii(0.25g,0.42mmol)的MeOH-DCM(分别为0.50和10mL)的冰冷溶液吹扫10min,并将混合物室温搅拌16h。蒸发溶剂并使用MeOH和Et_2O的混合物研磨残留物以获得化合物2(0.225g,90%)。

[0721] 1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-6-(四氢呋喃-2-基甲氧基)-1,3-苯并噻唑-2基]脲(3)

[0722]



^{1}HNMR (DMSO-d_6,400 MHz):δ 10.63 (br s, 1H), 9.00 (s, 2H), 7.72 (m, 2H), 6.68 (m, 1H), 5.12 (s, 1H), 4.21 (m, 1H), 4.06 (m, 2H), 3.68 (m, 2H), 3.18 (m, 2H), 1.94 (m, 1H), 1.71 (m, 2H), 1.65 (m, 1H), 1.61 (s, 6H) 和 1.22 (t, *J*= 6.8 Hz, 3H).LCMS:458.20 $[M+H]^+$.

[0723] 2-((2-溴-4-硝基苯氧基)甲基)四氢呋喃(i):0℃下,向2-溴-1-氟-4-硝基-苯(5.0g,22.72mmol)的DMSO(40mL)的冰冷溶液中加入NaOH(1.36g,34.09mmol)和(四氢呋喃-2-基)甲醇(3.47g,34.09mmol)。将混合物室温搅拌1h,随后倒入水(50mL)中,使用1M HCl将pH调节至约7并使用EtOAc(2x250mL)萃取。合并的有机物用水、盐水洗涤、干燥(Na_2SO_4)、过滤并真空浓缩以获得i(6.50g,95%)。^{1}HNMR($CDCl_3$,400MHz):δ8.46(d,J=2.40Hz,1H),8.20(dd,分别为J=2.40和9.20Hz,1H),6.98(d,J=9.20Hz,1H),4.36(m,1H),4.16(m,2H)3.97(m,1H)3.86(m1H)2.07(m2H)和1.95(m2H)。

[0724] 3-溴-4-((四氢呋喃-2-基)甲氧基)苯胺(ii):室温下向i(5.5g,18.2mmol)的THF(30mL)溶液中加入二水合氯化亚锡(12.3g,54.6mmol)。将混合物在60℃下搅拌5h。将混合物倒入饱和的碳酸氢钠溶液(100mL)中并使用EtOAc(2x500mL)萃取。合并的有机物用水、盐水洗涤、干燥(Na_2SO_4)并真空浓缩。在二氧化硅上纯化粗残留物(50%EtOAc-己烷)以获得ii(4.0g,82%)。MS:272.0$[M+H]^+$。

[0725] 5-溴-6-((四氢呋喃-2-基)甲氧基)苯并[d]噻唑-2-胺(iii):室温下向ii(3.0g,11.62mmol)的乙酸(50mL)溶液中加入硫氰酸铵(4.18g,55.11mmol)。将得到的混合物室温搅拌15min,随后加入溴(0.68mL,13.22mmol)的乙酸(5mL)溶液。将混合物室温搅拌5h,然后使用氨溶液将pH调节至>7,随后使用EtOAc(2x200mL)萃取。合并的有机物用水和盐水洗涤、干燥(Na_2SO_4)并真空浓缩。在二氧化硅(60%EtOAc-己烷)上纯化残留物以获得iii(1.0g,26%)。^{1}HNMR(DMSO-d_6,400MHz):δ7.50(s,1H),7.49(s,1H),7.43(br s,2H),4.18(m,1H),3.96(m,2H),3.80(m,1H),3.69(m,1H),1.96(m,2H)和1.78(m,2H)。MS:329.0$[M+H]^+$。

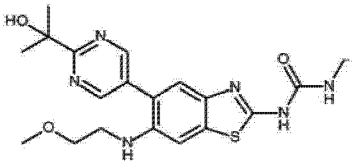
[0726] 1-(5-溴-6-((四氢呋喃-2-基)甲氧基)苯并[d]噻唑-2-基)-3-乙基脲(iv):室温下向iii(1.0g,3.03mmol)的1,4-二噁烷(10mL)溶液中加入异氰酸乙酯(1.23mL,15.19mmol)。将混合物80℃搅拌5h。真空蒸发反应混合物,加入水(50mL)并将混合物70℃搅拌4h。过滤残留物并真空吹干以获得iv(1.0g,83%)。^{1}HNMR(DMSO-d_6,400MHz):δ10.69(br s,1H),7.80(s,1H),7.68(s,1H),6.65(m,1H),4.21(m,1H),4.04(m,2H),3.83(m,1H),3.70(m,1H),3.16(m,2H),2.0(m,2H),1.82(m,2H)和1.09(t,J=7.20Hz,3H)。MS400$[M+H]^+$。

[0727] 1-乙基-3-(5-(2-(2-羟基丙-2-基)嘧啶-5-基)-6-((四氢呋喃-2-基)甲氧基)苯并[d]噻唑-2-基)脲(3):室温下向iv(0.303g,0.75mmol)和前体1的4,4,5,5-四甲基-1,3,2-二氧杂合成氧化铝(dioxaborolon)-2-基)酯(0.20g,0.75mmol)的1,4-二噁烷:MeOH(5:3,8.0mL)溶液中加入磷酸钾(0.24g,1.13mmol)。混合物用N_2吹扫15-20min以脱气,然后加入Pd(dppf)Cl_2(0.062g,0.075mmol)。将混合物脱气15-20min,然后在80℃加热5h。将反应混合物冷却至室温,使用EtOAc(500ml)稀释并通过硅藻土过滤。真空蒸发滤液并在二氧化硅上(5%MeOH-DCM)纯化粗残留物,以获得化合物3(0.15g,43%)。

[0728] 1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-6-(2-甲氧基乙基氨基)-1,3-苯并噻唑-2-基]脲(150)

[0729] 化合物150的制备方法与化合物3类似,从1-[5-溴-6-(2-甲氧基乙基氨基)-1,3-苯并噻唑-2-基]-3-乙基-脲和2-甲氧基乙胺开始。

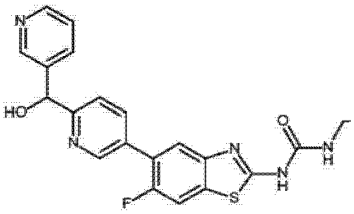
[0730]



^{1}H NMR (400 MHz; DMSO-d_6): 10.46-8.75 (m, 2H), 8.85 (d, 1H), 7.34 (s, 1H), 7.23 (s, 1H), 6.65 (d, 1H), 5.13-7.14 (m, 2H), 4.87 (br, 2H), 3.48 (s, 1H), 3.17-3.24 (m, 4H), 1.55 (s, 3H), 1.08 (s, 3H), 1.48 (s, 6H). LRMS [M+H] = 386.2MS 431.16 [M+H]$^+$

[0731] 1-乙基-3-(6-氟-5-(6-(羟基(吡啶-3-基)甲基)吡啶-3-基)苯并[d]噻唑-2-基)脲(4)

[0732]

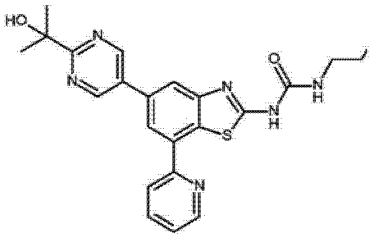


^{1}H NMR (400 MHz; DMSO-d_6):δ 8.67 (m, 2H), 8.45 (d, J= 3.60 Hz, 1H), 8.05 (m, 1H), 7.95 (m, 1H), 7.73-7.81 (m, 3H), 7.35 (m, 1H), 6.74 (m, 1H), 6.36 (d, J= 4.0 Hz, 1H), 5.85 (d, J= 4.0 Hz, 1H), 3.38 (m, 1H), 3.21 (m, 2H) 和 1.08 (t, J= 7.20 Hz, 3H).MS:424.31 [M+H]$^+$

[0733] 向前体80(0.2g,0.6mmol)的1,4-二噁烷(5mL)和MeOH(3mL)溶液中加入中间体13(0.2g,0.6mmol)和磷酸钾(0.2g,0.96mmol)。将反应物通过N_2吹扫脱气15min,然后加入Pd(dppf)Cl_2(0.05g,0.06mmol)。将化合物脱气10min并80℃加热4h。蒸发溶剂,加入水(50mL)并使用EtOAc(4x50mL)萃取混合物。合并的有机层用盐水洗涤、干燥(Na_2SO_4)并真空浓缩。在二氧化硅上纯化残留物,使用含2.50%MeOH的DCM洗脱以获得化合物4(0.02g,10%)。

[0734] 1-(2-羟基乙基)-3-(5-(2-(2-羟基丙烷-2-基)嘧啶-5-基)-7-(吡啶-2-基)苯并[d]噻唑-2-基)脲(5)

[0735]



^{1}H NMR (400 MHz; CD_3OD) δ = 9.14 (s, 2H), 8.70 (d, J = 4.3 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.10 (s, 1H), 7.97 -7.82 (m, 2H), 7.42 -7.25 (m, 1H), 3.75 (t, J = 5.5 Hz, 2H), 3.46 (t, J = 5.5 Hz, 2H), 1.69 (s, 6H).MS:451.08 [M+H]$^+$

[0736] [2-氨基-7-(2-吡啶基)-1,3-苯并噻唑-5-基]三氟甲磺酸酯(i):将[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]三氟甲磺酸酯(1.34g,3.0mmol)溶解在DMSO(10mL)中,并在160℃搅拌16h。使用EtOAc稀释混合物,并使用水和盐水洗涤。真空浓缩有机部分以生成i(1.01g,90%)。MS:375.96[M+H]$^+$。

[0737] [2-(2-羟基乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]三氟甲磺酸酯(ii):将化合物i(445mg,1.18mmol)溶解在DMF(7mL)中,并在0℃和氩气下,逐滴搅

拌加入 CDI(577mg,3.56mmol) 的 DMF(3mL) 溶液。将混合物升温至室温并搅拌 16h。随后加入乙醇胺 (710μL,11.85mmol) 的 DMF(2mL) 溶液,并将混合物室温搅拌 4h。使用 EtOAc 稀释混合物并使用水和盐水洗涤。对有机部分干燥 (Na_2SO_4) 并真空浓缩。使用 MeOH 和 Et_2O 洗涤残留物以得到 ii(253mg,46%)。MS:463.00[M+H]$^+$。

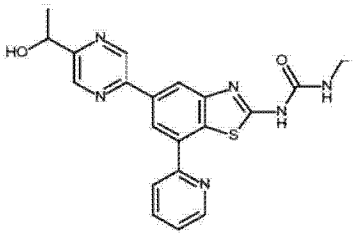
[0738] 2-[5-(4,4,5,5-四甲基-1,3,2-氧杂环戊硼烷-2-基)嘧啶-2-基]丙-2-醇 (iii):将前体 1(140mg,0.645mmol)、双频哪醇合二硼 (197mg,0.774mmol) 和乙酸钾 (95mg,0.967mmol) 悬浮在无水 1,4-二噁烷 (5mL) 中。加入三环己基膦 (23mg,0.081mmol) 和 $Pd_2(dba)_3$(30mg,0.032mmol),并通过氩气对混合物进行脱气/吹扫 (x3)。在微波辐射下将反应混合物 100℃搅拌 1h。将反应冷却至室温,过滤并使用 1,4-二噁烷 (5mL) 洗涤以获得 iii。MS:182.96[M+H]$^+$(硼酸)。

[0739] 1-(2-羟基乙基)-3-(5-(2-(2-羟基丙烷-2-基)嘧啶-5-基)-7-(吡啶-2-基)苯并[d]噻唑-2-基)脲 (5):向 iii(165mg,0.626mmol) 的 1,4-二噁烷 (12mL) 溶液中加入 ii(193mg,0.417mmol) 和 $PdCl_2$(dppf)(34mg,0.042mmol)。加入 Cs_2CO_3(410mg,1.30mmol) 的水 (3mL) 溶液,密封反应容器并用氩气排气/吹扫 (x3)。随后在微波辐射下将混合物在 100℃加热 30min。LCMS 分析显示了完全转换。混合物用 EtOAc(100mL) 稀释,用水、盐水洗涤,随后分离并干燥 (Na_2SO_4)。真空浓缩有机部分。在二氧化硅上通过色谱纯化,使用 0-10% MeOH/EtOAc 洗脱,随后在二氧化硅硅上通过额外的色谱纯化,使用 0-10% MeOH/DCM 洗脱以得到化合物 5(9mg,5%)。

[0740] 通用方法 B 的实施例

[0741] 1-乙基-3-[5-[5-(1-羟基乙基)吡嗪-2-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲 (6)

[0742]



^{1}H NMR (400 MHz; d_6-DMSO):δ = 10.70 (bs, 1H), 9.43 (d, J = 1.5 Hz, 1H), 8.96 -8.78 (m, 2H), 8.71 (d, J = 1.5 Hz, 1H), 8.47 (t, J = 5.3 Hz, 2H), 8.14 -7.94 (m, 1H), 7.49 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.88 (bt, J = 5.4 Hz, 1H), 5.65 (d, J = 4.7 Hz, 1H), 5.00 -4.84 (m, 1H), 3.29 -3.15 (m, 2H), 1.50 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).MS:421.08 [M+H]$^+$.

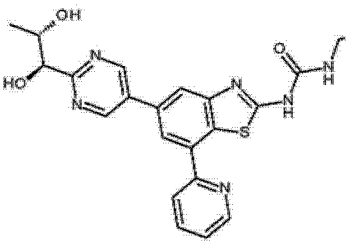
[0743] 1-[5-(5-乙酰吡嗪-2-基)-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲 (i):将中间体 1(171mg,0.5mmol)、1-(5-氯吡嗪-2-基)乙酮 (94mg,0.60mmol) 和 $PdCl_2$(dppf)(41mg,0.05mmol) 悬浮于 1,4-二噁烷 (8mL) 中。加入 Cs_2CO_3(488mg,1.50mmol) 的水 (2mL) 溶液。随后在微波辐射下将混合物在 100℃加热 30min。将混合物过滤,用水、EtOH、MeOH 和 Et_2O 洗涤以得到 i(172mg,82%)。MS:419.06[M+H]$^+$。

[0744] 1-乙基-3-(5-(5-(1-(羟基乙基)吡嗪-2-基)-7-(吡啶-2-基)苯并[d]噻唑-2-基)脲 (6):向 i(63mg,0.15mmol) 的 THF(5mL) 悬浮液中加入 $NaBH_4$(29mg,0.75mmol) 的水 (1mL) 溶液,并将混合物室温搅拌 30min。使用 EtOAc(50mL) 稀释反应并使用水和盐水洗涤。使有机部分干燥 (Na_2SO_4) 并真空浓缩以获得化合物 6(62mg,98%)。

[0745] 通用方法 C 的实施例

[0746] 1-[5-[2-[(1S*,2R*)-1,2-二羟基丙基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲(7)

[0747]



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 2H), 8.70 (s, 1H), 8.14 - 7.90 (m, 2H), 7.82 (t, J = 7.3 Hz, 1H), 7.75 (s, 1H), 7.30 (d, J = 10.5 Hz, 1H), 4.55 (s, 1H), 4.14 (d, J = 7.2 Hz, 1H), 3.23 (s, 2H), 1.42 (d, J = 3.9 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H).MS:451.1 $[M+H]^+$.

[0748] (5-溴嘧啶-2-基)甲醇(i):0℃下将$NaBH_4$(510mg,2.70mmol)的水(10mL)溶液逐滴引入到5-溴嘧啶-2-羧酸甲酯(3.05g,14.1mmol)的THF(100mL)溶液中。使混合物缓慢升温至室温过夜。蒸发大部分THF并使用EtOAc(200mL)稀释所得残留物。有机部分使用盐水(200mL)洗涤、干燥($MgSO_4$)并在二氧化硅上纯化,使用0-60% EtOAc:正庚烷洗脱以获得i(510mg,19%)。MS189.0和191.0;1:1$[M+H]^+$。

[0749] 5-溴-2-(溴甲基)嘧啶(ii):0℃下,将甲磺酰氯(0.31mL,4.0mmol)加入搅拌的i(510mg,2.7mmol)和三乙胺(820μL,5.9mmol)的THF(30mL)悬浮液中并持续10min。使用LiBr(1.2g,13mmol)的THF(25mL)溶液处理该溶液,并搅拌,同时在1h内升温至室温。真空除去大部分反应溶剂并使用EtOAc(200mL)稀释混合物。有机部分依次使用饱和NH_4Cl水溶液(2x100mL)、盐水(1x100mL)洗涤,并干燥($MgSO_4$)以获得ii(663mg,98%)。MS:251.0,253.0和254.8;1:2:1$[M+H]^+$。

[0750] 5-溴-2-(二乙氧基磷酰基甲基)嘧啶(iii):将化合物ii(663mg,2.63mmol)溶解在10mL的ACN中,并加入三乙基亚磷酸酯(0.92mL,5.26mmol)。在微波炉中将反应在100℃加热1h。真空浓缩反应以获得iii(813mg,100%)。MS:308.9和310.9;1:1$[M+H]^+$。

[0751] 1-[5-[2-(二乙氧基磷酰基甲基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲(iv):将中间体1(860mg,2.5mmol)、iii(813mg,2.63mmol)、Cs_2CO_3(2.57g,7.90mmol)和$Pd(PPh_3)_2Cl_2$(90mg,0.10mmol)溶解在1-4-二噁烷:水(10:1;10mL)中,并使用N_2气流脱气10min。在N_2气氛下密封反应并在微波反应器中在100℃加热1h。真空浓缩混合物,在二氧化硅上纯化(梯度洗脱:0-10% DCM-MeOH)并由丙酮研磨以得到iv(410mg,29%)。MS:527.1$[M+H]^+$。

[0752] 1-乙基-3-[5-[2-[(E)-亚丙-1-烯基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲(v):将甲醇钠(0.5M的MeOH溶液;0.9mL,0.43mmol)逐滴加入iv(104mg,0.198mmol)的THF(10mL)悬浮液中。加入乙醛(40μL,0.69mmol)并将混合物搅拌90min。用EtOAc(60mL)稀释反应并使用饱和$NaHCO_3$水溶液(60mL)洗涤。对有机部分干燥($MgSO_4$),真空浓缩并在二氧化硅上纯化(梯度洗脱:0-10%,DCM-MeOH)以获得v(79mg,96%)。MS:417.1$[M+H]^+$。

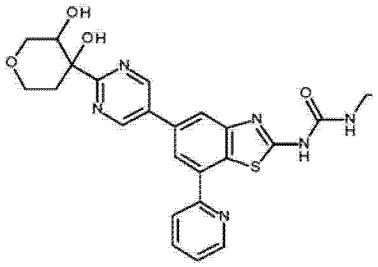
[0753] 1-[5-[2-[(1S*,2R*)-1,2-二羟基丙基]嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]-3-乙基-脲(7):将四氧化锇(10mg;60μmol)加入v(230mg,600μmol)、N-甲基吗啉-N-氧化物(160mg;1.40mmol)和吡啶(20μL)的THF-Me_2CO(5:1;90mL)溶液中。使用饱和$Na_2S_2O_5$水溶液(20mL)终止反应,使用EtOAc(150mL)萃取,使用盐水(75mL)洗涤,干燥($MgSO_4$)并真空浓缩。在二氧化硅上纯化(梯度洗脱:0-10%,DCM-MeOH)以得

到化合物 7(93mg,38%)。

[0754] 通用方法 D 的实施例

[0755] 1-(5-(2-(3,4- 二羟基四氢 -2H- 吡喃 -4- 基)嘧啶 -5- 基)-7-(吡啶 -2- 基)苯并[d]噻唑 -2- 基)-3- 乙基脲 (8)

[0756]



^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 9.34 (s, 2H), 8.83 (dd, J = 4.8, 0.8 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.4 Hz, 1H), 8.15 (d, J = 0.9 Hz, 1H), 8.02 (td, J = 7.9, 1.8 Hz, 1H), 7.53 - 7.41 (m, 1H), 6.94 - 6.77 (m, 1H), 5.41 (s, 1H), 4.76 (t, J = 7.5 Hz, 1H), 3.93 (d, J = 11.0 Hz, 2H), 3.82 - 3.70 (m, 2H), 3.69 - 3.62 (m, 1H), 3.28 - 3.15 (m, 2H), 2.69 - 2.55 (m, 1H), 1.81 (d, J = 13.8 Hz, 1H), 1.12 (t, J = 7.2 Hz, 3H).MS:493.1, $[M+H]^+$.

[0757] 5- 溴 -2-(3,6- 二氢 -2H- 吡喃 -4- 基)嘧啶 (i):将 5- 溴 -2- 碘 - 嘧啶 (250mg;0.88mmol) 和 2-(3,6- 二氢 -2H- 吡喃 -4- 基)-4,4,5,5- 四甲基 -1,3,2- 二氧杂环戊硼烷 (196mg,0.92mmol) 溶解在 1,4- 二噁烷 - 水 (10:1;10mL) 中,并使用 N_2 气流脱气 10min。加入 $Pd(Ph_3)_2Cl_2$(30mg,0.04mmol) 并将反应密封,并在 80℃的微波反应器中加热 30min。真空浓缩反应物,重新溶解在 DCM 中,过滤并在二氧化硅上纯化(梯度洗脱:0-50% EtOAc- 正庚烷)以生成 i(105mg,50%)。MS:241.1 和 243.0;1:1$[M+H]^+$。

[0758] 5- 溴 -2-(3,7- 二氧杂二环 [4.1.0] 庚烷 -6- 基)嘧啶 (ii):将化合物 i(105mg;0.436mmol) 溶解在 DCM(15mL) 中并冷却至 0℃,随后加入固体 3- 氯苯过氧羧酸 (280mg,1.14mmol) 并将混合物搅拌过夜。使用 1M $Na_2S_2O_3$ 水溶液 (5mL) 终止反应并依次使用饱和 $NaHCO_3$ 水溶液 (3x30mL) 和盐水 (1x30mL) 洗涤。对有机部分进行干燥 ($MgSO_4$)。在二氧化硅上通过色谱纯化并使用 0-50% EtOAc- 正庚烷洗脱以得到 ii(20mg,18%)。MS:256.9 和 258.8;1:1$[M+H]^+$。

[0759] 1-[5-[2-(3,7- 二氧杂二环 [4.1.0] 庚烷 -6- 基)嘧啶 -5- 基]-7-(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-3- 乙基 - 脲 (iii):将中间体 1(29mg,0.085mmol)、ii(20mg,78μmol)、Cs_2CO_3(55mg0.17mmol) 和 $Pd(Ph_3)_2Cl_2$(3mg,4μmol) 溶解在 1,4- 二噁烷:水 (10:1,10mL) 中。混合物使用 N_2 气流脱气 10min,随后在 80℃的微波反应器内加热 1h。真空浓缩反应,重新将其溶解在最少量的 DCM 中,并在二氧化硅上通过色谱纯化 (0-10% DCM-MeOH) 以生成 iii(23mg57%)。MS:475.0,$[M+H]^+$。

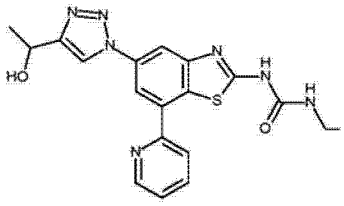
[0760] 1-(5-(2-(3,4- 二羟基四氢 -2H- 吡喃 -4- 基)嘧啶 -5- 基)-7-(吡啶 -2- 基)苯并[d]噻唑 -2- 基)-3- 乙基脲 (8):将化合物 iii(20mg;0.042mmol) 溶解在 THF- 水 (10:1,11mL) 中。加入浓硫酸 (20μL) 和对甲苯磺酸 (0.7mg,4μmol) 并在室温搅拌混合物。真空浓缩混合物并在二氧化硅上纯化 (0-100% 0.1% FA 水溶液 - MeCN) 以生成化合物 8(8.8mg,42%)。

[0761] 通用方法 E 的实施例

[0762] 1- 乙基 -3-[5-[4-(1- 羟基乙基)三唑 -1- 基]-7-(2- 吡啶基)-1,3- 苯并噻

唑-2-基]脲(9)

[0763]



^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (br s, 1H), 8.91 (s, 1H), 8.84 (d, J = 3.9 Hz, 1H), 8.46 (d, J = 8.2 Hz, 1H), 8.41 (s, 1H), 8.16 (s, 1H), 8.03 (td, J = 7.9, 1.8 Hz, 1H), 7.49 (dd, J = 7.2, 5.2 Hz, 1H), 7.02 (br s, 1H), 5.41 (d, J = 4.8 Hz, 1H), 5.00 - 4.92 (m, 1H), 3.26 - 3.15 (m, 2H), 1.52 (d, J = 6.5 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H).MS:410.0 $[M+H]^+$.

[0764] 1-(5-叠氮基-7-溴-1,3-苯并噻唑-2-基)-3-乙基脲(i):将中间体3(3.0g,7.04mmol)、叠氮化钠(930mg,14.08mmol)、L-抗坏血酸钠(350mg,1.8mmol)和CuI(120mg;0.63mmol)溶解在DMSO(100mL)和水(24mL)的混合物中。加入N,N'-二甲基乙烷-1,2-二胺(100mg,1.1mmol),并将悬浮液在100℃加热过夜。加入水并通过过滤收集所得固体。使用水清洗并真空干燥以获得i(1.68g)。MS:342.9$[M+H]^+$。

[0765] 1-{7-溴-5-[4-(二乙氧基甲基)-1H-1,2,3-三唑-1-基]-1,3-苯并噻唑-2-基}-3-乙基-5-甲基-1,3,5-三嗪-2-酮(ii):将化合物i(1.68g,4.89mmol)悬浮在MeOH(65mL)中,随后依次加入甲醛(37wt%水溶液,7.94g,97.9mmol)和甲基胺(2M,MeOH中;24.5mL,49mmol)。将悬浮液加热至80℃持续5h。加入水,并依次用EtOAc和DCM对混合物进行萃取。将有机层干燥(Na_2SO_4)、过滤并真空浓缩,以获得包含1-(5-叠氮-7-溴-1,3-苯并噻唑-2-基)-3-乙基-5-甲基-1,3,5-三嗪-2-酮的残留物(1.31g)。将该混合物的一部分(827mg;2.09mmol)悬浮在DMF(36mL)中,在0℃冷却,随后用3,3-二乙氧基丙-1-炔(535mg,4.17mmol)、DIPEA(320mg,2.5mmol)和CuI(70mg;0.37mmol)处理。移开冰浴并使得反应在室温搅拌过夜。冻干混合物,并在二氧化硅(DCM中0-5%MeOH梯度)上通过色谱纯化残留物以获得残留物,使用EtOAc对该残留物进行研磨以得到ii(354mg,13%)。^{1}H NMR(400MHz,DMSO-d_6) δ 8.90(s,1H),8.26(d,J = 1.8Hz,1H),8.10(d,J = 1.8Hz,1H),5.75(s,1H),5.13(s,2H),4.40(s,2H),3.63(qq,J = 9.6,7.1Hz,4H),3.38(q,J = 7.1Hz,2H),2.55(s,3H),1.18(t,J = 7.1Hz,6H),1.13(t,J = 7.1Hz,3H)。

[0766] 1-{5-[4-(二乙氧基甲基)-1H-1,2,3-三唑-1-基]-7-(吡啶-2-基)-1,3-苯并噻唑-2-基}-3-乙基-5-甲基-1,3,5-三嗪-2-酮(iii):将化合物ii(415mg,0.79mmol)悬浮在DMF(5mL)中并加入三丁基(2-吡啶基)锡烷(250mg,1.68mmol)。通过在真空下将反应容器冻干并回充氩气的方式对混合物进行脱气。加入CuI(30mg,0.2mmol)和$Pd(PPh_3)_2Cl_2$(1:2)(60mg,0.08mmol)。使用氩气对混合物进行脱气并在110℃加热过夜。通过硅藻土过滤混合物,使用DMF洗涤。冻干滤液以获得残留物,在二氧化硅上(庚烷中的0-100%EtOAc梯度)通过色谱纯化该残留物,以得到iii(250mg,60%)。^{1}H NMR(400MHz,DMSO-d_6) δ 9.06(br s,1H),8.85(ddd,J = 4.8,1.7,0.9Hz,1H),8.53(d,J = 2.0Hz,1H),8.52-8.49(m,1H),8.30(d,J = 2.0Hz,1H),8.06-8.01(m,1H),7.49(ddd,J = 7.5,4.9,0.9Hz,1H),5.79(s,1H),5.16(s,2H),4.39(s,2H),3.72-3.59(m,4H),3.40(q,J = 7.1Hz,2H),2.56(s,3H),1.20(t,J = 7.1Hz,6H),1.14(t,J = 7.1Hz,3H)。MS:523.0$[M+H]^+$。

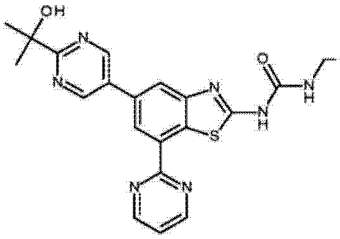
[0767] 1-乙基-3-[5-(4-甲酰基-1H-1,2,3-三唑-1-基)-7-(吡啶-2-基)-1,3-苯并噻唑-2-基]脲(iv):将化合物iii(250mg,0.48mmol)悬浮于1M HCl溶液(9mL)中并将混合物在70℃加热过夜。真空浓缩混合物以获得iv(213mg,定量)。MS:394.0$[M+H]^+$。

[0768] 1-乙基-3-{5-[4-(1-羟基乙基)-1H-1,2,3-三唑-1-基]-7-(吡啶-2-基)-1,3-苯并噻唑-2-基}脲(9):向iv(40mg,0.1mmol)的THF(0.7mL)悬浮液中加入3M的溴化(甲基)镁的Et_2O(0.250mL,0.1mmol)溶液,并将混合物在40℃加热1h。加入NH_4Cl(饱和水溶液)并使用DCM:IPA(5:1)对混合物进行萃取。使用盐水洗涤有机层,随后真空浓缩以获得粗产物,通过反相SP4纯化(水中的CAN梯度)该粗产物,以得到化合物9(1.9mg,4%)。

[0769] 通用方法F的实施例

[0770] 1-乙基-3-(5-(2-(2-羟基丙-2-基)嘧啶-5-基)-7-(嘧啶-2-基)苯并[d]噻唑-2-基)脲(10)

[0771]



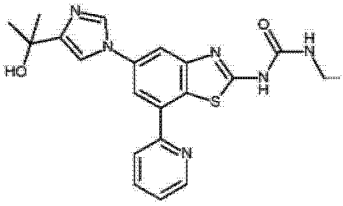
^{1}H NMR (DMSO-d_6):δ10.72 (br s, 1H), 9.24 (s, 2H), 9.08 (d, *J*= 4.80 Hz, 2H), 8.70 (s, 1H), 8.23 (s, 1H), 7.57 (t, *J*= 4.80 Hz, 1H), 6.82 (m, 1H), 5.17 (s, 1H), 3.22 (m, 2H), 1.56 (s, 6H) 和 1.12 (t, *J*= 7.20 Hz, 3H).MS:436.15 $[M+H]^+$.

[0772] 用N_2吹扫对中间体5(0.30g,0.68mmol)和2-(三丁基锡烷基)嘧啶(0.253g,0.68mmol)的DMF(10mL)溶液进行脱气15min,随后加入$Pd(PPh_3)_4$(0.078g,0.06mmol)。用N_2吹扫对混合物脱气10min,随后加热至80℃持续16h。向反应中加入冰水,随后用EtOAc(3x100mL)萃取。合并的有机物用盐水洗涤、干燥(Na_2SO_4)、过滤并真空浓缩。在二氧化硅(2.50% MeOH-DCM)上纯化残留物以获得化合物10(0.015g,5%)。

[0773] 通用方法G的实施例

[0774] 1-乙基-3-(5-(4-(2-羟基丙烷-2-基)-1H-咪唑-1-基)-7-(吡啶-2-基)苯并[d]噻唑-2-基)脲(11)

[0775]



^{1}H NMR (400 MHz, MeOD) δ 8.73 (d, J = 4.8 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.20 (d, J = 1.4 Hz, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.92 (td, J = 7.9, 1.8 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.55 (d, J = 1.4 Hz, 1H), 7.37 (dd, J = 7.5, 4.9 Hz, 1H), 3.37 - 3.32 (m, 2H), 1.62 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H).MS:422.99 $[M+H]^+$.

[0776] 2-(1H-咪唑-4-基)丙-2-醇)(i):

[0777] 将1H-咪唑-4-羧酸甲酯(430mg)在HMDS(1mL)中回流加热30min,随后蒸馏除去过量的HMDS。在将残留物溶解于THF中前,将其置于真空下并用N_2吹扫两次。将溶液冷却至0℃并在0℃下逐滴加入MeMgBr(4.5mL;3M)并将混合物升温至室温过夜。使用1mL饱和NH_4Cl终止反应,随后用2-3mL水稀释。将混合物真空浓缩成水性乳液,并将其加入12g

C18 反相柱中。使用 100% ACN 洗脱以获得残留物，在二氧化硅上通过色谱进一步纯化该残留物，使用 MeOH/DCM 洗脱以得到 i(280mg)。

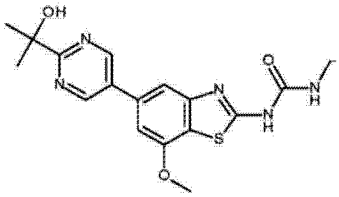
[0778] 1- 乙基 -3-(5-(4-(2- 羟基丙烷 -2- 基)-1H- 咪唑 -1- 基)-7-(吡啶 -2- 基) 苯并 [d] 噻唑 -2- 基) 脲 (11)：使用4Å分子筛将化合物 i(74mg) 和中间体 1(100mg) 悬浮在吡啶中。使用氧气对混合物进行脱气和吹扫，并加入 $Cu(OAc)_2.H_2O$。对混合物再次使用氧气进行脱气和吹扫，随后在 80℃下搅拌 280min。加入饱和 NH_4Cl 终止反应，随后用 EtOAc 和水稀释。混合物用 EtOAc 萃取，并合并有机相，干燥 (Na_2SO_4) 并蒸发至干。在二氧化硅上通过色谱纯化，使用 DCM/MeOH(0-10%) 洗脱，随后在 C18 柱上进行反相色谱，使用 ACN/ 水洗脱以得到化合物 11(7.5mg)。

[0779] 进一步官能化的实施例

[0780] 羟基基团的烷基化

[0781] 1- 乙基 -3-(5-(2-(2- 羟基丙烷 -2- 基) 嘧啶 -5- 基)-7- 甲氧基苯并 [d] 噻唑 -2- 基) 脲 (12)

[0782]



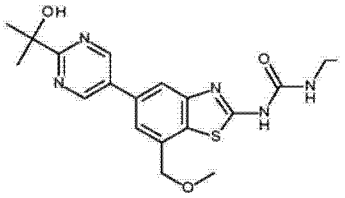
^{1}H NMR (400 MHz, Acetone-d_6) δ 9.22 (d, J = 2.7 Hz, 2H), 7.65 (s, 1H), 7.22 (s, 1H), 4.11 (s, 3H), 3.44 - 3.26 (m, 2H), 1.60 (s, 6H), 1.19 (t, J = 7.2 Hz, 3H).MS:388.03 $[M+H]^+$.

[0783] 将中间体 9(240mg) 和 Cs_2CO_3(220mg) 的无水 DMF(10mL) 溶液冷却至 0℃，随后使用碘甲烷 (83.5mg) 处理。使反应在 90min 内升温至室温，随后使用水终止反应。真空浓缩混合物并将所得的残留物悬浮在 DCM 和最少量的 MeOH 中，用于在二氧化硅 (0-5% MeOH:DCM) 上通过色谱进行纯化。将残留物悬浮在 THF(10mL) 中并使用 1M HCl(10mL) 进行处理。反应在室温搅拌 90min，随后使用 $NaHCO_3$ 溶液中和。使用 EtOAc(15mL) 稀释混合物，在水性层和有机层之间形成白色固体。通过过滤收集固体并真空干燥同时在 50℃下加热以得到化合物 12(83mg)。

[0784] 通过醛由卤素部分形成醚

[0785] 1- 乙基 -3-(5-(2-(2- 羟基丙烷 -2- 基) 嘧啶 -5- 基)-7-(甲氧基甲基) 苯并 [d] 噻唑 -2- 基) 脲 (13)

[0786]



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 2H), 7.95 (s, 1H), 7.23 (s, 1H), 4.67 (s, 2H), 3.48 (dd, J = 12.1, 6.3 Hz, 2H), 3.44 (s, 3H), 1.63 (s, 6H), 1.33 - 1.21 (m, 3H).MS 402.04 $[M+H]^+$.

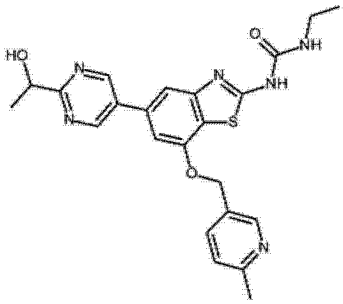
[0787] 2-(3- 乙基 -5- 甲基 -2- 氧代 -1,3,5- 三嗪 -1- 基)-5-[2-(1- 羟基 -1- 甲基 - 乙基) 嘧啶 -5- 基]-1,3- 苯并噻唑 -7- 醛 (i)：在 N_2 下将中间体 4(200mg,0.41mmol) 的 THF(10mL) 溶液冷却至 -80℃，随后使用 nBuLi(0.89mL,1.22mmol) 进行处理。1min 后加入 DMF(0.06mL,0.81mmol) 并使反应在 30min 内升温至室温。使用 $NaHCO_3$(20mL) 稀释反应，随后使用 EtOAc(2x15mL) 进行萃取。对有机萃取物进行干燥 ($MgSO_4$)，过滤并浓缩。将

残留物悬浮在 DCM 中，随后在二氧化硅上通过色谱纯化，使用 0-5% MeOH:DCM 洗脱以得到 i(38.5mg,22%)。MS441.01[M+H]$^+$。

[0788] 1-乙基-3-(5-(2-(2-羟基丙烷-2-基)嘧啶-5-基)-7-(甲氧基甲基)苯并[d]噻唑-2-基)脲：使用 H_2SO_4(20mL,0.38mmol) 处理 i(23mg,0.05mmol) 的 MeOH(2mL) 溶液，随后室温搅拌 90min。使用 $NaHCO_3$ 中和反应，随后使用 EtOAc(2x10mL) 萃取。对有机萃取物进行干燥 ($MgSO_4$)，过滤并浓缩。将粗材料悬浮于 DCM(2mL) 中并使用三乙基硅烷 (50μL,0.31mmol) 和 BF_3OEt_2(25μL,0.20mmol) 进行处理。反应在室温下搅拌 30min，使用 MeOH(2mL) 终止反应并搅拌 1h。混合物使用 EtOAc(5mL) 稀释并使用 $NaHCO_3$(5mL) 和水 (5mL) 洗涤。对有机萃取物进行干燥 ($MgSO_4$)，过滤并浓缩。将材料悬浮于 MeCN:MeOH 中，并通过反相色谱 (5-40-50-100% MeCN:H_2O+0.1% FA) 纯化，以获得化合物 13(7.3mg,21%)。

[0789] 1-乙基-3-(5-(2-(1-(羟基乙基)嘧啶-5-基)-7-((6-甲基吡啶-3-基)甲氧基)苯并[d]噻唑-2-基)脲(14)

[0790]



^{1}H NMR (400 MHz, D_2O) δ 8.60 (s, 2H), 8.29 (s, 1H), 8.15 (d, J = 7.0 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 6.91 (s, 1H), 6.38 (s, 1H), 3.03 - 2.90 (m, 2H), 2.75 (s, 3H), 1.45 (t, J = 10.7 Hz, 3H), 1.00 (dt, J = 14.1, 7.1 Hz, 3H).MS:465.1 [M+H]$^+$.

[0791] 1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[(6-甲基-3-吡啶基)甲氧基]-1,3-苯并噻唑-2-基]-5-甲基-1,3,5-三嗪-2-酮(i)：0℃下将甲磺酰氯 (120μL；1.50mmol) 逐滴加入 (6-甲基-3-吡啶基)甲醇 (100mg；0.812mmol) 和三乙胺 (0.32mL；2.25mmol) 的无水 DCM(6mL) 溶液中，并在 0℃下持续搅拌 30min。使用 MeOH(2mL) 终止反应，真空浓缩并在二氧化硅(梯度洗脱，50-100%，正庚烷-EtOAc) 上纯化，以形成 (6-甲基-3-吡啶基)甲基甲磺酸酯 (95mg,58%)。

[0792] 在一个独立的烧瓶内，室温下将中间体 10(45mg,0.11mmol)and K_2CO_3(68mg,0.49mmol) 溶解在 DMF(10mL) 中并加入 (6-甲基-3-吡啶基)甲基甲磺酸酯 (95mg,0.47mmol) 的 DMF(3mL) 溶液。将反应加热至 45℃持续 3h。将反应混合物浓缩至其初始体积的 1/3 并使用 EtOAc(100mL) 稀释，依次使用水 (100mL) 和盐水 (100mL) 洗涤，并使用 DCM:IPA(5:1,100mL) 反萃取水相，随后在二氧化硅上通过色谱纯化，使用含 0-10% DCM 的 MeOH 洗脱以得到 i(30mg,53%)。

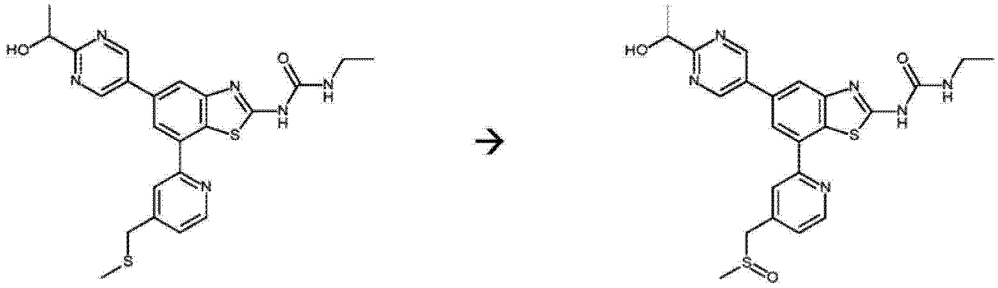
[0793] 1-乙基-3-(5-(2-(1-(羟基乙基)嘧啶-5-基)-7-((6-甲基吡啶-3-基)甲氧基)苯并[d]噻唑-2-基)脲(14)：将化合物 i(30mg；58μmol) 悬浮在 THF(3mL) 中，加入浓 HCl(1mL) 并加热至 45℃持续 1.5h。真空浓缩反应并通过反相色谱纯化，在 1M HCl(ca.3mL) 存在的条件下梯度洗脱 (25-80%，含 0.1% FA(水性)的 ACN) 并冻干以得到化合物 14(23mg,79%)。

[0794] 由硫醚形成砜

[0795] 1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(甲基硫烷基甲基)-2-吡

啶基]-1,3-苯并噻唑-2-基]脲(15);和1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-[4-(甲基亚磺酰基甲基)-2-吡啶基]-1,3-苯并噻唑-2-基]脲(16)

[0796]

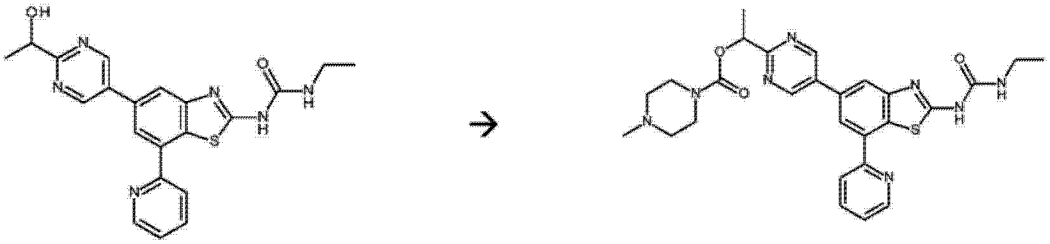


[0797] 室温下将过硫酸氢钾制剂(45mg,0.073mmol)的水(0.5mL)溶液加入化合物15(70mg,0.146mmol)的DMF(4.5mL)溶液中并搅拌1h。混合物使用EtOAc(50mL)稀释并使用水洗涤。水性部分使用NaCl饱和并使用EtOAc(3x50mL)再次萃取。对合并的有机层干燥(Na_2SO_4)并真空浓缩。在二氧化硅上通过色谱纯化残留物,使用0-30%MeOH/EtOAc洗脱以得到化合物16(15mg,21%)。MS:496.97$[M+H]^+$;^{1}H NMR(400MHz;d_6-DMSO):δ=10.79(bs,1H),9.36(s,2H),8.87(d,J=4.9Hz,1H),8.52(s,1H),8.39(d,J=1.5Hz,1H),8.20(d,J=1.5Hz,1H),7.47(dd,J=5.1,1.2Hz,1H),7.03(bd,J=5.2Hz,1H),5.35(d,J=5.5Hz,1H),4.94(p,J=6.5Hz,1H),4.36(d,J=12.5Hz,1H),4.25-4.07(m,1H),3.28(dd,J=7.1,5.7Hz,2H),2.64(s,3H),1.54(d,J=6.6Hz,3H),1.18(t,J=7.2Hz,3H)。

[0798] 通用方法H的实施例

[0799] 1-乙基-3-[5-[2-(1-羟基乙基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲(17);和1-(5-(2-(3-乙基脲基)-7-(吡啶-2-基)苯并[d]噻唑-5-基)嘧啶-2-基)乙基4-甲基哌嗪-1-羧酸酯(18)

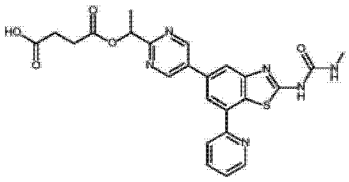
[0800]



[0801] 将按照与化合物1(0.2378mmol;100mg)的制备方法类似的方法制备的化合物17溶解在DMF(1mL)中并加入二(咪唑-1-基)甲酮(0.26mmol;42mg)并室温搅拌18h。加入1-甲基哌嗪(0.29mmol;29mg)并将混合物室温搅拌18h。真空浓缩混合物并在二氧化硅上通过色谱纯化残留物,使用0-12% MeOH/DCM洗脱,随后通过反相色谱以获得甲酸盐形式存在的化合物18(12mg)。^{1}HNMR(400MHz,DMSO-d_6)δ10.69(s,1H),9.39(s,2H),8.84(d,J=4.0Hz,1H),8.55(d,J=8.2Hz,1H),8.42(d,J=1.4Hz,1H),8.18(d,J=1.1Hz,1H),8.03(td,J=7.9,1.7Hz,1H),7.48(dd,J=7.1,5.1Hz,1H),6.92(t,J=5.2Hz,1H),4.54(d,J=12.9Hz,1H),4.36(d,J=12.9Hz,1H),3.27-3.18(m,2H),2.77(s,3H),1.14(t,J=7.2Hz,3H)。MS453.01$[M+H]^+$。

[0802] 4-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙氧基]-4-氧代-丁酸(19)

[0803]

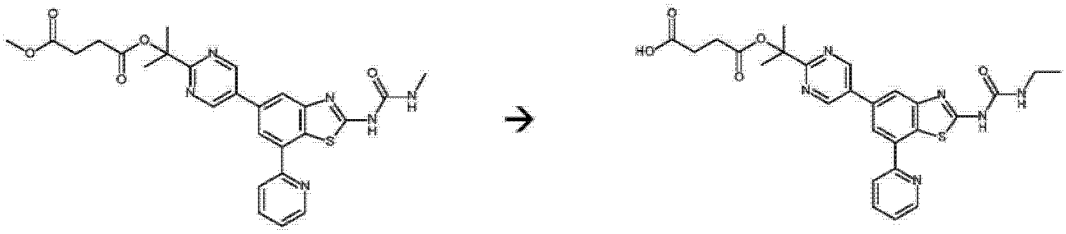


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 2H), 8.70 - 8.63 (m, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.83 - 7.67 (m, 3H), 7.20 - 7.13 (m, 1H), 5.83 (q, J = 6.8 Hz, 1H), 3.30 - 3.13 (m, 2H), 2.63 (dd, J = 6.8, 2.1 Hz, 2H), 2.52 (dd, J = 6.5, 2.9 Hz, 2H), 1.57 (d, J = 6.8 Hz, 3H), 1.09 (t, J = 7.3 Hz, 2H).MS 521.09 $[M+H]^+$.

[0804] 使用DIPEA(230mg)、DMAP(40mg)和琥珀酸酐(150mg)处理化合物17(250mg)的溶液,随后50℃搅拌6h。随后加入DIPEA(300μL)和琥珀酸酐(100mg),反应搅拌过夜。混合物用水(30mL)稀释并用EtOAc(3x15mL)洗涤。对水性萃取物进行浓缩以获得粗棕色胶状物质。在二氧化硅上通过色谱纯化,使用含0-5%MeOH的DCM洗脱以获得固体,将该固体悬浮于热的MeOH中,使之冷却至室温并通过过滤收集所得固体并真空干燥以获得化合物19。

[0805] O4-[1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]-1-甲基-乙基]O1-甲基丁二酸酯(20);和4-((2-(5-(2-(3-乙基脲基)-7-(吡啶-2-基)苯并[d]噻唑-5-基)嘧啶-2-基)丙-2-基)氧基)-4-氧代丁酸(21)

[0806]

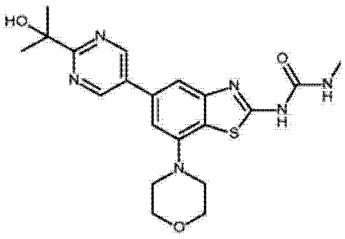


[0807] 将按照与化合物1(179mg,0.33mmol)的制备方法类似的方法制备的化合物20溶解在MeOH(18mL)中并加入NaOH(0.65mL,1M,水溶液)。室温下搅拌溶液,随后在1.5h和3.5h后加入额外的NaOH(0.65mL,1M,水溶液)。7h后加入水(0.5mL)。将溶液室温搅拌过夜。23h后,使用HCl(1M,水溶液)将混合物酸化至pH4.5,将溶液真空浓缩至干,与ACN(3x20mL)共沸。在二氧化硅上通过色谱纯化固体,使用含0-5%MeOH的DCM洗脱,随后在二氧化硅上进一步通过色谱纯化,使用含0-5%MeOH的EtOAc洗脱并在二氧化硅上进一步通过色谱纯化,使用含0-5%MeOH的DCM洗脱以获得化合物21(47mg,27%)。^{1}H NMR(400MHz,MeOD):δ9.14(s,2H),8.77(ddd,J = 4.3,1.7,0.8Hz,1H),8.29(d,J = 7.8Hz,1H),8.19(d,J = 1.5Hz,1H),7.99(d,J = 1.5Hz,1H),7.96(dt,J = 7.8 和 1.7Hz,1H),7.40(ddd,J = 7.4,4.3,0.8Hz,1H),3.37(q,J = 7.2Hz,2H),2.71(m,2H),2.60(m,2H),1.87(s,6H),1.27(t,J = 7.2Hz,3H)。MS:535.05$[M+H]^+$。

[0808] 通用方法I的实施例

[0809] 1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-吗啉基-1,3-苯并噻唑-2-基]脲(151)

[0810]



^{1}H NMR (400 MHz; DMSO-d_6):δ 10.75 (br s, 1H), 9.16 (s, 2H), 7.72 (s, 1H), 7.16 (s, 1H), 6.73 (m, 1H), 5.11 (s, 1H), 3.86 (m, 4H), 3.17-3.26 (m, 6H), 1.54 (s, 6H) 和 1.09 (t, J= 7.20 Hz, 3H).MS:443.28 $[M+H]^+$

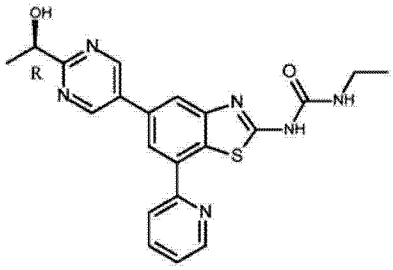
[0811] 1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-吗啉基-1,3-苯并噻唑-2-基]-5-甲基-1,3,5-三嗪-2-酮(i):向中间体4(0.25g,0.51mmol)的1,4-二噁烷(10mL)溶液中依次加入吗啉(0.066g,0.77mmol)和Cs_2CO_3(0.25g,0.77mmol)。用氮气吹扫所得的溶液30min,之后加入$Pd_2(dba)_3$(0.026g,0.025mmol)和Xantphos(0.035g,0.061mmol)。再用氮气吹扫所述反应混合物15min,然后加热至80℃过夜。反应完成后(TLC监测),将反应冷却至室温,通过硅藻土床过滤,使用EtOAc洗涤硅藻土床,并在减压条件下浓缩合并的滤液。随后在硅胶(100-200M,3%MeOH-DCM)上纯化粗残留物以获得灰白色固体状的i(0.07g,28%)。^{1}H NMR(DMSO-d_6,400MHz):δ9.18(s,2H),7.79(s,1H),7.19(s,1H),5.12(s,3H),4.37(s,2H),3.80-3.83(m,4H),3.35-3.38(m,2H),3.21-3.23(m,4H),2.54(s,3H),1.54(s,6H)和1.08(t,J=6.80Hz,3H)。

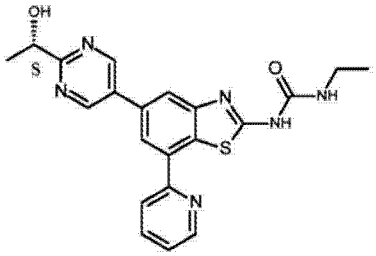
[0812] 1-乙基-3-[5-[2-(1-羟基-1-甲基-乙基)嘧啶-5-基]-7-吗啉基-1,3-苯并噻唑-2-基]脲(151):向冰冷的i(0.065g,0.13mmol)的THF(3mL)溶液中加入6N-HCl(2mL)。将混合物室温搅拌4h。反应完成后(TLC监测),将混合物倒入饱和$NaHCO_3$溶液中,随后用EtOAc(2x50mL)萃取。合并的有机物用盐水洗涤,在无水Na_2SO_4上干燥,过滤并且减压浓缩。使用MeOH-Et_2O研磨所得残留物以得到白色固体状的化合物151(0.035g,61%)。

[0813] 手性分离和合成的实施例

[0814] (R)-1-乙基-3-(5-(2-(1-羟基乙基)嘧啶-5-基)-7-(吡啶-2-基)苯并[d]噻唑-2-基)脲(22)和(S)-1-乙基-3-(5-(2-(1-羟基乙基)嘧啶-5-基)-7-(吡啶-2-基)苯并[d]噻唑-2-基)脲(23)

[0815]





[0816] 通过手性制备型HPLC分离化合物17的(R)和(S)对映异构体:

[0817] 柱: Chiralpak IC(250x20mm)5μ

[0818] 流动相: 100%MeOH

[0819] 样品细节: 25mg,在0.5mL TFA和0.5mL MeOH的混合物中

[0820] 流速: 18mL/min。

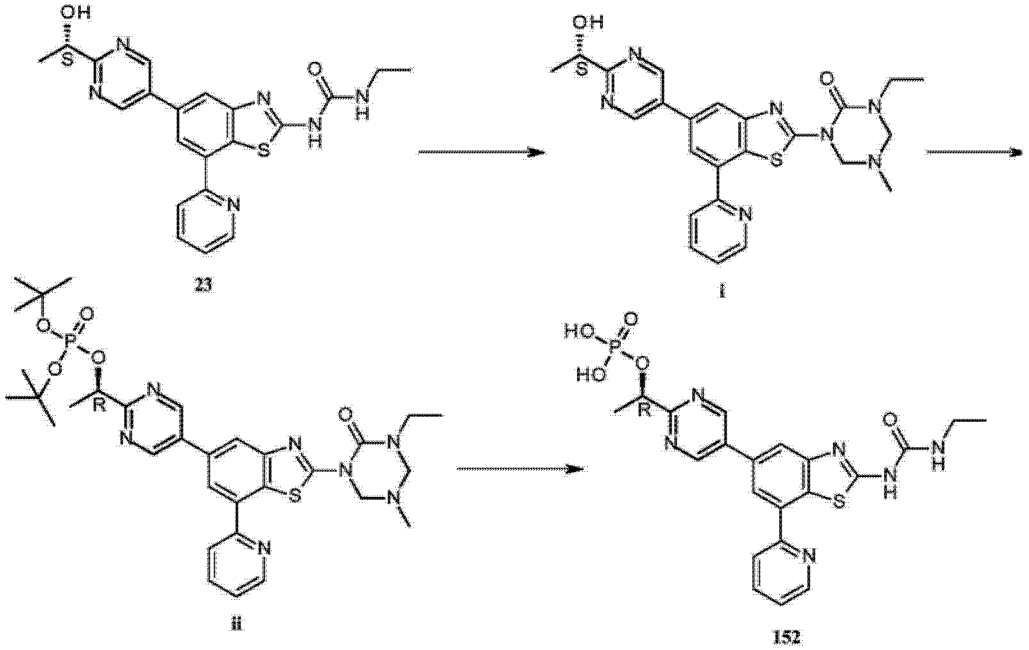
[0821] 运行时间: 20min。

[0822] 保留时间: 9.3min;14.7min。

[0823] [(1R)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧

啶 -2- 基] 乙基] 磷酸二氢酯 (152) ;和 [(1S)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基] 磷酸二氢酯 (153)

[0824]



[0825] 1- 乙基 -3-[5-[2-(-(1S)-1- 羟基乙基) 嘧啶 -5- 基]-7-[(2- 吡啶基)-1,3- 苯并噻唑 -2- 基]-5- 甲基 -1,3,5- 三嗪 -2- 酮 (i) :将化合物 23(12.67g,30.13mmol) 悬浮在 MeOH(150mL) 中。加入甲醛 (48.9mL,0.603mol,37 % 水溶液) 以及 N- 甲基吗啉 (33.1mL,0.301mol) 和甲基胺 (151mL,2M 的 THF 溶液)。将白色悬浮液在 70℃加热过夜。19 小时后 TLC 显示几乎完全转化成产物,将溶液冷却至室温,随后减压浓缩至约 33%的体积并在水 (150mL) 和 EtOAc(300mL) 之间分配。对双相混合物加热以帮助产物溶解。有机层用盐水洗涤,通过 $MgSO_4$ 过滤并减压浓缩至干。固体用 EtOAc(100mL) 冲刷,过滤,使用 EtOAc 和庚烷洗涤并干燥以获得白色固体状的 i(11.97g,76%)。MS:475.93$[M+H]^+$。

[0826] [(1R)-1-[5-[2-(3- 乙基 -5- 甲基 -2- 氧代 -1,3,5- 三嗪 -1- 基)-7-(2- 吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基] 磷酸二叔丁酯 (ii) :

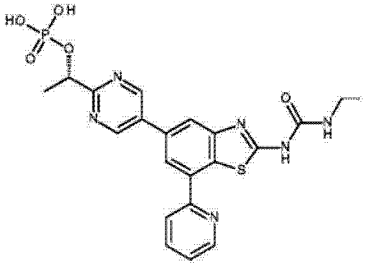
[0827] 磷酸氢二叔丁酯的制备 :将磷酸二叔丁酯钾盐 (45g) 溶解在水 (160mL) 中。加入盐酸 (1M,水溶液) 直至 pH 为约 3。通过过滤收集所得沉淀,使用水洗涤并真空干燥过夜以获得白色固体状的二叔丁基膦酸。随后,加入 i(18.68g,39.28mmol)、三苯基膦 (17.51g,66.78mmol) 和磷酸氢二叔丁酯 (10.73g,51.06mmol) 的 THF 悬浮液中,且三苯基膦悬浮于无水 THF(200mL) 中。逐滴加入 DIAD(13.5g,66.78mmol) 的 THF(20mL) 溶液。室温搅拌混合物并通过 LCMS 监测至完成,随后减压浓缩。加入 Et_2O(300mL) 并对混合物进行超声,得到亮白色固体,对其进行过滤,使用 Et_2O(100mL) 洗涤并空气干燥。滤液也包含一些产物。浓缩至 150mL 后,将滤液置于冰中冷却,生成更多的固体材料。收集固体材料,将其重新溶解在 DCM 中并通入 (50-100 % EtOAc/DCM 以除去光延副产物,随后通入 10 % MeOH/DCM 以洗脱所需的产物。在将相关部分浓缩为白色固体后,从 DCM/ 醚 / 庚烷中重新结晶该材料,过滤,使用庚烷洗涤 , 并干燥过夜以得到白色固体状的 ii(17.09g,64 %)。^1H NMR(400MHz) δ 9.41(s,2H) ;8.83(d,J = 4.4Hz,1H) ;8.53(d,J =

8Hz,1H) ;8.43(d,J = 1.2Hz,1H) ;8.21(d,J = 1.2Hz,1H) ;8.01(dt,J = 8,1.6Hz,1H) ;7.46(dd,J = 7.2,4.8Hz) ;5.43(m,1H) ;5.16(s,2H) ;4.38(s,2H) ;3.39(q,J = 7.2Hz,2H) ;3.32(br s,2H) ;2.55(s,3H) ;1.64(d,J = 6.8Hz,3H) ;1.38(s,9H) ;1.36(s,9H) ;1.14(t,J = 7.2Hz)。MS:667.78$(M+H)^+$。手性 HPLC:柱:Chirapak IC,0.46cm x25cm;25min 等度梯度,100% MeOH,保留时间= 17.12min。

[0828] [(1R)-1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3-苯并噻唑-5-基]嘧啶-2-基]乙基]磷酸二氢酯(152):使用含 4M HCl 的二噁烷(63.6mL,10 当量)处理 ii(17.0g,25.46mmol)的无水 THF(300mL)溶液。加入酸后立即形成沉淀,通过 LCMS 监测反应至完成。加入水(50mL)并将溶液浓缩以除去约 150mL 的 THF,此时絮凝状沉淀开始形成。将混合物在室温搅拌过夜,生成白色沉淀,对其进行过滤,用水洗涤数次,随后用 MeOH 和 Et_2O 洗涤,然后在 50℃下干燥 6 小时以生成白色固体状的化合物 152(12.0g,95%)。MS:501.7$[M+H]^+$。^1H NMR(400MHz,DMSO-d_6):δ 10.7(br s1H),9.35(s,2H),8.85-8.81(m,1H),8.53(d,J = 8.3Hz,1H),8.39(d,J = 1.6Hz,1H),8.15(d,J = 1.6Hz,1H),8.05-7.99(m,1H),7.49-7.44(m,1H),6.93(t,J = 5.5Hz,1H),5.48-5.39(m,1H),3.27-3.17(m,2H),1.63(d,J = 6.6Hz,3H),1.12(t,J = 7.2Hz,3H)。

[0829] 可以类似方法从化合物 22 起始制备化合物 153。

[0830]



^1H NMR (400 MHz, DMSO-d_6):δ 10.6 (br s, 1H), 9.35 (s, 2H), 8.85 – 8.81 (m, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.56 – 7.31 (m, 1H), 6.89 (t, J = 5.5 Hz, 1H), 5.47 – 5.38 (m, 1H), 3.26 – 3.18 (m, 2H), 1.63 (d, J = 6.6 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).MS:501.05 $[M+H]^+$.

[0831] 参考前文所述通用方法和/或实施例使用类似方法制备下列化合物。

[0832] 表 1:化合物和表征数据

[0833]

No.	观察到的 LCMS $[M+H]^+$	^1H NMR
24	486	(DMSO-d_6): δ 10.62 (s, 1H), 9.0 (s, 1H), 8.8 (d, 1H), 8.5 (d, 1H), 8.4 (d, 1H), 8.35 (s, 1H), 8.05 (m, 2H), 7.8 (s, 1H), 7.5 (m, 1H), 7.1 (s, 1H), 6.9 (s, 1H), 6.8 (s, 1H), 6.3 (d, 1H), 6.0 (d, 1H), 3.7 (s, 3H), 3.25 (m, 2H), 1.15 (t, 3H)
25	534.15	($CDCl_3$): δ 9.22 (s, 2H), 8.66 (s, 1H), 8.13 (s, 1H), 7.89 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.77 (s, 1H), 3.84 – 3.67 (m, 4H), 3.58 (s, 2H), 3.41 (s, 2H), 2.51 (s, 4H), 1.61 (s, 6H), 1.31 – 1.26 (m, 3H).

[0834]

26	**518.17**	($CDCl_3$) δ 9.18 (s, 2H), 8.66 (d, J = 4.7 Hz, 1H), 8.46 (s, 1H), 8.16 (s, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 3.92 (s, 2H), 3.51 – 3.36 (m, 2H), 2.80 (s, 4H), 1.92 (s, 4H), 1.63 (s, 6H), 1.35 – 1.22 (m, 3H).
27	**434.05**	($CDCl_3$) δ 8.91 (d, J = 1.6 Hz, 1H), 8.59 (d, J = 4.5 Hz, 1H), 8.12 – 7.98 (m, 4H), 7.82 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.21 (dd, J = 7.2, 5.0 Hz, 1H), 3.56 – 3.43 (m, 2H), 1.59 (s, 6H), 1.32 (t, J = 7.2 Hz, 3H).
28	**534.18**	(DMSO-d_6) δ 10.63 (br s, 1H)；9.35 (s, 2H)；8.77 (d, J = 5 Hz, 1H)；8.44 (1H, s)；8.39 (1H, s)；8.15 (1H, s)；7.47 (d, J = 5 Hz, 1H)；6.90 (br s, 1H)；5.15 (s, 1H)；3.66 (s, 2H)；3.63 (s, 4H)；3.23 (m, 2H)；2.46 (s, 4H)；1.59 (s, 6H)；1.14 (t, J = 7 Hz, 3H). 亚甲基磺酸盐形式：^{1}H NMR (400 MHz; D_2O): δ = 8.70 (s, 2H), 8.25 (s, 1H), 7.83 (s, 1H), 7.34 (s, 1H), 7.17 (s, 2H), 4.28 (s, 2H), 4.00 (s, 4H), 3.33 (s, 4H), 3.21–3.02 (m, 2H), 2.83 (s, 3H), 1.66 (s, 6H), 1.12 (t, *J* = 7.2 Hz, 3H). MS: 534.19 $[M+H]^+$ HCl 盐形式：^{1}H NMR (400 MHz; DMSO-d_6): δ = 12.24 (bs, 1H), 9.45 (s, 2H), 9.11 (s, 1H), 8.92 (d, *J* = 5.0 Hz, 1H), 8.55 (d, *J* = 1.5 Hz, 1H), 8.22 (d, *J* = 1.5 Hz, 1H), 7.66 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.20 (bs, 1H), 4.54 (s, 2H), 3.96 (s, 4H), 3.46–3.29 (m, 2H), 3.29–3.09 (m, 4H), 1.59 (s, 6H), 1.14 (t, *J* = 7.2 Hz, 3H). MS: 534.18 $[M+H]^+$
29	**534.3**	(DMSO-d_6) δ 10.80 (br s, 1H), 9.32 (s, 2H), 8.75 (d, J= 4.80 Hz, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.12 (s, 1H), 7.42 (d, J= 4.80 Hz, 1H), 7.05 (m, 1H), 5.16 (br s, 1H), 4.74 (br s, 1H), 4.22 (br s, 1H), 3.67-3.78 (m, 2H), 3.38 (m, 2H), 3.17-3.24 (m, 2H), 2.73-2.75 (m, 1H), 2.63-2.67 (m, 1H), 2.37-2.40 (m, 1H), 2.01-2.06 (m, 1H), 1.56 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).
30	**520.25**	(DMSO-d_6) δ 10.67 (br s, 1H), 9.33 (s, 2H), 8.73 (d, J= 4.80 Hz, 1H), 8.36 (br s, 2H), 8.12 (s, 1H), 7.35 (d, J= 4.80 Hz, 1H), 6.92 (m, 1H), 5.35 (d, J= 6.40 Hz, 1H), 5.15 (s, 1H), 4.21-4.26 (m, 1H), 3.71 (s, 2H), 3.58 (t, J= 6.40 Hz, 2H), 3.21 (m, 2H), 2.85 (t, J= 6.40 Hz, 2H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).
31	**534.28**	(DMSO-d_6) δ 10.62 (br s, 1H), 9.35 (s, 2H), 8.73 (d, J= 4.80 Hz, 1H), 8.38 (m, 2H), 8.13 (s, 1H), 7.35 (d, J= 4.80 Hz, 1H), 6.86 (m, 1H), 5.15 (s, 1H), 4.0-4.03 (m, 1H), 3.74 (s, 2H), 3.57 (t, J= 6.40 Hz, 2H), 3.21 (m, 2H), 3.15 (s, 3H), 2.93 (m, 2H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).
32	**564.3**	(DMSO-d_6) δ 10.62 (br s, 1H), 9.33 (s, 2H), 8.61 (d, J= 5.60 Hz, 1H), 8.40 (s, 1H), 8.12 (s, 1H), 8.03 (s, 1H), 7.05 (m, 1H), 6.90 (m, 1H), 5.15 (s, 1H), 4.34 (t, J= 5.60 Hz, 2H), 3.57-3.59 (m, 4H), 3.31-3.36 (m, 4H), 3.19-3.22 (m, 2H), 2.76 (t, J= 5.60 Hz, 2H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).

[0835]

33	**548.31**	(DMSO-d_6) δ 10.61 (br s, 1H), 9.33 (s, 2H), 8.76 (d, J= 4.80 Hz, 1H), 8.39 (s, 2H), 8.13 (s, 1H), 7.42 (m, 1H), 6.85 (m, 1H), 5.15 (s, 1H), 3.53-3.58 (m, 5H), 3.18-3.25 (m, 2H), 2.50 (m, 2H), 2.32 (m, 2H), 1.57 (s, 6H), 1.38 (d, J= 6.80 Hz, 3H), 和 1.11 (t, J= 7.20 Hz, 3H).
34	**554.25**	(DMSO-d_6) δ 10.63 (br s, 1H), 9.33 (s, 2H), 8.76 (d, J= 4.80 Hz, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 8.14 (s, 1H), 7.43 (m, 1H), 6.86 (m, 1H), 5.16 (s, 1H), 3.79 (s, 2H), 3.18-3.24 (m, 2H), 2.92-2.99 (m, 2H), 2.78 (t, J= 6.80 Hz, 2H), 2.23-2.34 (m, 2H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).
35	**536.28**	(DMSO-d_6) δ 10.63 (br s, 1H), 9.32 (s, 2H), 8.75 (d, J= 4.80 Hz, 1H), 8.50 (s, 1H), 8.38 (s, 1H), 8.13 (s, 1H), 7.42 (d, J= 4.80 Hz, 1H), 6.86 (t, J= 5.20 Hz, 1H), 5.15 (m, 2H), 3.78 (s, 2H), 3.18-3.33 (m, 2H), 2.80-2.89 (m, 2H), 2.66-2.68 (m, 1H), 2.39-2.50 (m, 1H), 2.12-2.19 (m, 1H), 1.89-1.98 (m, 1H), 1.56 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).
36	**536.26**	(DMSO-d_6) δ 10.62 (br s, 1H), 9.32 (s, 2H), 8.75 (d, J= 4.80 Hz, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 8.13 (s, 1H), 7.43 (d, J= 4.80 Hz, 1H), 6.86 (t, J= 5.20 Hz, 1H), 5.15 (m, 2H), 3.78 (s, 2H), 3.19-3.23 (m, 2H), 2.80-2.89 (m, 2H), 2.64-2.76 (m, 1H), 2.41-2.45 (m, 1H), 2.11-2.21 (m, 1H), 1.85-1.96 (m, 1H), 1.56 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).
37	**568.3**	(DMSO-d_6) δ 10.64 (br s, 1H), 9.32 (s, 2H), 8.77 (d, J= 5.20 Hz, 1H), 8.41 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 7.36-7.42 (m, 1H), 6.88 (m, 1H), 5.16 (s, 1H), 3.76 (s, 2H), 3.12-3.25 (m, 4H), 2.72 (t, J= 11.20 Hz, 2H), 1.86-1.93 (m, 2H), 1.69 (m, 2H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).
38	**578.31**	(DMSO-d_6) δ 10.60 (br s, 1H), 9.33 (s, 2H), 8.61 (d, J= 5.60 Hz, 1H), 8.38 (s, 1H), 8.12 (s, 1H), 8.01 (s, 1H), 7.04 (m, 1H), 6.86 (m, 1H), 5.15 (s, 1H), 4.26 (t, J= 6.0 Hz, 2H), 3.57 (m, 4H), 3.17-3.24 (m, 2H), 2.44-2.46 (m, 2H), 2.37 (br s, 4H), 1.91-1.98 (m, 2H), 1.56 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).
39	**436.19**	(DMSO-d_6) δ 10.78 (br s, 1H), 9.81 (s, 1H), 9.36 (s, 2H), 8.89 (s, 1H), 8.71 (s, 1H), 8.56 (s, 1H), 8.22 (s, 1H), 6.92 (m, 1H), 5.16 (s, 1H), 3.21 (m, 2H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H)
40	**437**	($CDCl_3$) δ 9.04 (s, 2H), 8.79 – 8.71 (m, 1H), 8.04 – 7.76 (m, 4H), 7.31 – 7.26 (m, 3H), 4.94 (t, J = 4.5 Hz, 1H), 4.02 (ddd, J = 25.6, 11.5, 4.5 Hz, 2H), 3.34 (dd, J = 3.3, 1.6 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H).
41	**429.98**	($CDCl_3$) δ 8.87 (1 H, d, J = 1.8 Hz), 8.13 (1 H, dd, J = 8.2 and 1.8 Hz), 7.74 (1 H, s), 7.46 (1 H, d, J = 8.2 Hz), 3.87 (2 H, s), 3.46 (2 H, m), 2.44 (6 H, s), 1.64 (6 H, s), 1.30 (3 H, t, J = 7.2 Hz).

[0836]

42	**548.34**	(DMSO-d_6) δ 9.32 (s, 2H), 8.75 (d, J= 5.20 Hz, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.12 (s, 1H), 7.41 (d, J= 4.80 Hz, 1H), 6.90 (m, 1H), 5.15 (s, 1H), 3.90 (m, 1H), 3.77 (s, 2H), 3.21 (m, 3H), 3.15 (s, 3H), 2.72-2.76 (m, 1H), 2.59-2.65 (m, 1H), 2.54 (m, 1H), 1.97-2.04 (m, 1H), 1.57-1.72 (m, 1H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).
43	**450.24**	(DMSO-d_6) δ 10.70 (br s, 1H), 9.34 (s, 2H), 9.27 (s, 1H), 8.55 (m, 2H), 8.25 (s, 1H), 6.83 (m, 1H), 5.16 (s, 1H), 3.21 (m, 2H), 2.60 (s, 3H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H)
44	**471.96**	($CDCl_3$) δ 10.8 (1 H, br s), 8.91 (1 H, d, J = 1.9 Hz), 8.11 (1 H, dd, J = 8.2 and 1.9 Hz), 7.78 (1 H, s), 7.48 (1 H, dd, J = 8.2 and 0.6 Hz), 4.98 (1 H, br s), 3.92 (2 H, s), 3.80 (4 H, br s), 3.47 (2 H, m), 2.70 (4 H, br s), 1.65 (6 H, s), 1.30 (3 H, t, J = 7.3 Hz).
45	**574.20 [M-H]$^-$**	(DMSO-d_6) δ 12.43 (br s, 1H), 10.82 (br s, 1H), 9.24 (s, 2H), 8.54 (s, 1H), 7.94-8.0 (m, 2H), 7.66 (s, 1H), 7.03 (m, 1H), 6.77 (m, 1H), 5.14 (br s, 1H), 4.01-4.04 (m, 2H), 3.15-3.25 (m, 4H), 2.0-2.04 (m, 2H), 1.55 (s, 6H), 1.40-1.45 (m, 2H), 1.19 (s, 3H) 和 1.09 (t, J=7.20 Hz, 3H).
46	**493.21**	(DMSO-d_6) δ 10.74 (br s, 1H), 9.32 (s, 2H), 8.69 (s, 1H), 8.45 (d, J= 8.40 Hz, 1H), 8.36 (s, 1H), 8.12 (s, 1H), 7.89 (d, J= 8.40 Hz, 1H), 7.02 (m, 1H), 5.15 (s, 1H), 3.74 (s, 2H), 3.20-3.23 (m, 2H), 1.56 (s, 6H) 和 1.11 (t, J=7.20 Hz, 3H).
47	**475.1**	($CDCl_3$) δ 10.25 (s, 1H), 9.26 (s, 2H), 8.64 (dd, J = 4.6, 0.7 Hz, 1H), 7.77 – 7.60 (m, 3H), 7.54 (d, J = 17.3 Hz, 2H), 7.21 – 7.08 (m, 1H), 3.11 (dd, J = 18.7, 11.4 Hz, 2H), 1.64 – 1.50 (m, 2H), 1.48 – 1.29 (m, 4H), 1.26 (t, J = 7.3 Hz, 4H), 0.97 (t, J = 7.1 Hz, 3H).
48	**440.03**	($CDCl_3$) δ 8.79 (d, J = 4.3 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 8.00 (s, 1H), 7.96 (d, J = 1.0 Hz, 1H), 7.89 (s, 1H), 7.86 (dd, J = 7.9, 1.7 Hz, 1H), 7.33 (dd, J = 6.8, 5.0 Hz, 1H), 3.44 -3.37 (m, 3H), 1.78 (s, 6H), 1.32 (t, J = 7.3 Hz, 3H).
49	**435.12**	(DMSO-d_6) δ 10.68 (s, 1H), 9.44 – 9.33 (m, 1H), 9.08 – 8.97 (m, 1H), 8.85 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.70 (d, J = 1.5 Hz, 1H), 8.52 – 8.38 (m, 2H), 8.09 – 7.97 (m, 1H), 7.49 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 3.29 – 3.13 (m, 2H), 1.56 (s, 6H), 1.14 (dd, J = 9.3, 5.0 Hz, 3H).
50	**576.32**	(DMSO-d_6) δ 10.88 (br s, 1H), 9.32 (s, 2H), 8.34 (d, J= 5.60 Hz, 1H), 8.31 (s, 1H), 8.06 (s, 1H), 7.71 (br s, 1H), 7.28 (br s, 1H), 6.89 (m, 1H), 5.15 (br s, 1H), 3.84-3.87 (m, 2H), 3.14-3.34 (m, 4H), 2.07-2.10 (m, 2H), 1.56 (s, 6H), 1.34-1.44 (m, 2H), 1.15 (s, 3H) 和 1.11 (t, J= 7.20 Hz, 3H)

[0837]

51	**576.34**	(DMSO-d_6) δ 12.40 (br s, 1H), 10.67 (br s, 1H), 9.29 (s, 2H), 8.21 (s, 1H), 8.07 (s, 1H), 7.67-7.71 (m, 1H), 7.62-7.64 (m, 1H), 6.93 (m, 1H), 6.89 (m, 1H), 5.13 (s, 1H), 4.14-4.17 (m, 2H), 3.38 (m, 2H), 3.21-3.24 (m, 2H), 2.07-2.11 (m, 2H), 1.56 (s, 6H), 1.45-1.50 (m, 2H), 1.19 (s, 3H) 和 1.12 (t, J=7.20 Hz, 3H).
52	**577.38**	(DMSO-d_6) δ 12.50 (br s, 1H), 10.66 (br s, 1H), 9.22 (s, 2H), 8.61 (s, 1H), 8.42 (d, J= 6.0 Hz, 1H), 8.15 (s, 1H), 6.86-6.88 (m, 2H), 5.14 (s, 1H), 4.26-4.32 (m, 2H), 3.38 (m, 2H), 3.21-3.24 (m, 2H), 2.08-2.11 (m, 2H), 1.56 (s, 6H), 1.44-1.49 (m, 2H), 1.20 (s, 3H) 和 1.14 (t, J=7.20 Hz, 3H)
53	**504.11**	($CDCl_3$) δ 9.16 (s, 2H), 8.64 (s, 1H), 8.00 (s, 2H), 7.84 (s, 1H), 7.24 (d, J = 3.2 Hz, 1H), 4.02 (s, 2H), 3.64 – 3.19 (m, 2H), 2.29 (s, 1H), 1.62 (s, 6H), 1.28 (dd, J = 14.6, 7.4 Hz, 4H), 0.56 (d, J = 5.5 Hz, 3H).
54	**590.34**	(DMSO-d_6) δ 12.20 (br s, 1H), 10.55 (br s, 1H), 9.28 (s, 2H), 8.20 (d, J= 6.0 Hz, 1H), 8.06-8.11 (m, 2H), 7.36 (s, 1H), 6.89 (m, 1H), 6.55 (m, 2H), 5.15 (s, 1H), 3.50-3.52 (m, 2H), 3.15-3.24 (m, 2H), 2.50 (m, 1H), 2.03-2.10 (m, 2H), 1.86-1.94 (m, 2H), 1.56 (s, 6H), 1.29-1.38 (m, 2H) 和 1.09-1.13 (m, 6H).
55	**520.25**	(DMSO-d_6) δ 10.70 (br s, 1H), 9.32 (s, 2H), 8.75 (d, J= 4.40 Hz,1H), 8.37-8.42 (m, 2H), 8.12 (s, 1H), 7.43 (d, J= 4.40 Hz, 1H), 6.87 (m, 1H), 5.30 (d, J= 5.20 Hz,1H), 4.86 (m, 1H), 3.61-3.70 (m, 6H), 3.19 (m, 2H), 2.43-2.45 (m, 4H), 1.47 (d, J= 6.40 Hz, 3H) 和 1.11 (t, J=7.20 Hz, 3H).
56	**564.31**	(DMSO-d_6) δ 10.60 (br s, 1H), 9.31 (s, 2H), 8.52 (s, 1H), 8.45 (d, J= 8.80 Hz, 1H), 8.29 (s, 1H), 8.07 (s, 1H), 7.62 (m, 1H), 6.86 (m, 1H), 5.15 (s, 1H), 4.30 (t, J= 5.60 Hz, 2H), 3.59 (br s, 4H), 3.21 (m, 2H), 2.75 (t, J= 5.60 Hz, 2H), 2.45-2.50 (m, 4H), 1.56 (s, 6H) 和 1.09 (t, J= 7.20 Hz, 3H).
57	**449.11**	(DMSO-d_6) δ = 10.58 (bs, 1H), 9.35 (s, 2H), 8.84 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 1.3 Hz, 1H), 8.10–7.98 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.92 (bt, J = 5.5 Hz, 1H), 5.15 (s, 1H), 3.18 (dd, J = 13.0, 6.7 Hz, 2H), 1.59 (s, 6H), 1.53 (dd, J = 14.2, 7.3 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H).
58	**447.1**	(DMSO-d_6) δ 10.61 (s, 1H), 9.32 (s, 2H), 8.83 (d, J = 4.0 Hz, 1H), 8.53 (d, J = 8.2 Hz, 1H), 8.40 (d, J = 1.1 Hz, 1H), 8.14 (s, 1H), 8.02 (td, J = 8.1, 1.7 Hz, 1H), 7.46 (dd, J = 7.0, 5.2 Hz, 1H), 6.86 (d, J = 5.3 Hz, 1H), 5.28 (d, J = 6.0 Hz, 1H), 3.38 (dd, J = 14.0, 7.0 Hz, 2H), 1.42 – 1.28 (m, 1H), 1.12 (t, J = 7.0 Hz, 3H), 0.54 – 0.46 (m, 2H), 0.46 – 0.33 (m, 2H).
59	**435.1**	(DMSO-d_6) δ 10.62 (s, 1H), 9.32 (s, 2H), 8.90 – 8.76 (m, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.39 (d, J = 1.5 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 8.02 (td, J = 7.8, 1.8 Hz, 1H), 7.46 (ddd, J = 7.5, 4.9, 0.8 Hz, 1H), 6.87 (t, J = 5.3 Hz, 1H), 5.21 (d, J = 5.9 Hz, 1H), 4.63 (dt, J = 11.7, 5.8 Hz, 1H), 3.27 – 3.16 (m, 2H), 1.98 – 1.73 (m, 2H), 1.18 – 1.06 (m, 3H), 0.90 (t, J = 7.4 Hz, 3H).

[0838]

60	**463.1**	(DMSO-d_6) δ 10.62 (s, 1H), 9.33 (s, 2H), 8.83 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 8.08 – 7.95 (m, 1H), 7.46 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.86 (t, J = 5.5 Hz, 1H), 5.02 (d, J = 6.7 Hz, 1H), 4.44 (d, J = 6.8 Hz, 1H), 3.26 – 3.18 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H), 0.95 (s, 9H).
61	**449.1**	(DMSO-d_6) δ 10.59 (s, 1H), 9.32 (s, 2H), 8.83 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.4 Hz, 1H), 8.07 – 7.97 (m, 1H), 7.46 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.20 (d, J = 6.0 Hz, 1H), 4.70 (dt, J = 7.4, 5.8 Hz, 1H), 3.26 – 3.18 (m, 2H), 1.93 – 1.69 (m, 2H), 1.50 – 1.27 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H).
62	**520.06**	(MeOD) δ 9.21 (s, 2H), 8.77 (d, J = 3.1 Hz, 1H), 8.47 (s, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 1.5 Hz, 1H), 8.00 (d, J = 1.5 Hz, 1H), 7.95 (td, J = 7.8, 1.8 Hz, 1H), 7.40 (dd, J = 7.0, 5.3 Hz, 1H), 6.04 (q, J = 6.8 Hz, 1H), 3.87 (s, 1H), 3.35 (t, J = 3.6 Hz, 2H), 1.75 (d, J = 6.8 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.12 (d, J = 7.0 Hz, 6H).
63	**520.04**	(MeOD) δ 9.21 (s, 2H), 8.82 – 8.74 (m, 1H), 8.47 (s, 1H), 8.29 (d, J = 8.2 Hz, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.96 (ddd, J = 11.0, 9.8, 1.7 Hz, 2H), 7.44 – 7.35 (m, 1H), 6.02 (q, J = 6.8 Hz, 1H), 3.90 (d, J = 4.4 Hz, 1H), 3.36 (t, J = 7.2 Hz, 2H), 1.75 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 7.2 Hz, 3H), 1.13 (dd, J = 7.0, 2.1 Hz, 6H).
64	**522.3**	(DMSO-d_6) δ 10.62 (br s, 1H), 9.32 (s, 2H), 8.75 (d, J= 4.40 Hz, 1H), 8.37-8.43 (m, 2H), 8.13 (s, 1H), 7.42 (br s, 1H), 6.86 (m, 1H), 5.29 (s, 2H), 4.87 (br s, 1H), 3.78 (s, 2H), 3.21 (m, 2H), 2.80-2.83 (m, 2H), 2.66 (m, 1H), 1.93-2.18 (m, 3H), 1.47 (d, J= 6.0 Hz, 3H) 和 1.10 (t, J= 6.40 Hz, 3H).
65	**506.23**	(DMSO-d_6) δ 10.73 (br s, 1H), 9.32 (s, 2H), 8.72 (d, J= 4.80 Hz, 1H), 8.36 (m, 2H), 8.11 (s, 1H), 7.34 (m, 1H), 6.98 (m, 1H), 5.29-5.36 (m, 2H), 4.86-4.89 (m, 1H), 4.23 (m, 1H), 3.72 (s, 2H), 3.56 (m, 2H), 3.21 (m, 2H), 2.85 (m, 2H), 1.47 (d, J= 6.80 Hz, 3H) 和 1.11 (t, J=7.20 Hz, 3H).
66	**520.27**	(DMSO-d_6) δ 10.62 (br s, 1H), 9.32 (s, 2H), 8.72 (d, J= 4.80 Hz, 1H), 8.36 (m, 2H), 8.12 (s, 1H), 7.37 (m, 1H), 6.68 (m, 1H), 5.29 (d, J =5.6 Hz, 1H), 5.22 (br s, 1H), 4.87 (m, 1H), 3.74 (s, 2H), 3.19-3.26 (m, 4H), 2.97 (m, 2H), 1.47 (t, J= 6.80 Hz, 3H), 1.38 (s, 3H) 和 1.09 (t, J=7.20 Hz, 3H).
67	**548.3**	(DMSO-d_6) δ 12.18 (br s, 1H), 9.40 (s, 2H), 9.07 (s, 1H), 8.88 (br s, 1H), 8.58 (s, 1H), 8.20 (s, 1H), 7.65-7.70 (m, 1H), 7.28 (br s, 1H), 7.28 (s, 1H), 4.60 (m, 2H), 3.56 (m, 1H), 3.09-3.37 (m, 7H), 1.90- 2.01 (m, 2H) 1.57 (s, 6H) 和 1.06-1.21 (m, 5H).

[0839]

68	**534.14**	(DMSO-d_6) δ = 10.62 (s, 1H), 9.33 (s, 2H), 8.77 (d, J = 4.9 Hz, 1H), 8.42 (s, 1H), 8.37 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 7.47 (d, J = 5.1 Hz, 1H), 6.88 (t, J = 5.5 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.96–4.83 (m, 1H), 4.11 (d, J = 14.4 Hz, 1H), 3.67 (ddd, J = 10.7, 7.3, 3.2 Hz, 2H), 3.58–3.47 (m, 1H), 3.39 (d, J = 14.0 Hz, 1H), 3.27–3.19 (m, 3H), 2.61 (dt, J = 11.7, 2.6 Hz, 1H), 2.50-2.44 (m, 1H), 2.24 (ddd, J = 12.6, 9.8, 3.2 Hz, 1H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 1.06 (d, J = 6.3 Hz, 3H).
69	**548.18**	(DMSO-d_6) δ = 10.64 (s, 1H), 9.34 (s, 2H), 8.77 (d, J = 5.3 Hz, 1H), 8.43 (s, 1H), 8.38 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.4 Hz, 1H), 7.44 (dd, J = 5.0, 1.0 Hz, 1H), 6.90 (t, J = 5.4 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.97–4.83 (m, 1H), 3.70–3.57 (m, 4H), 3.28–3.17 (m, 2H), 2.75 (d, J = 10.2 Hz, 2H), 1.75 (t, J = 10.7 Hz, 2H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.3 Hz, 6H).
70	**528.18**	(DMSO-d_6) δ = 10.64 (bs, 1H), 9.34 (s, 2H), 8.84–8.71 (m, 1H), 8.43 (s, 1H), 8.38 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.4 Hz, 1H), 7.45 (dd, J = 5.1, 1.2 Hz, 1H), 6.90 (bt, J = 5.4 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.99–4.82 (m, 1H), 3.66 (s, 2H), 3.24 (tt, J = 12.9, 6.5 Hz, 2H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).
71	**548.19**	(DMSO-d_6) δ = 10.64 (bs, 1H), 9.33 (s, 2H), 8.77 (d, J = 5.0 Hz, 1H), 8.43 (d, J = 13.5 Hz, 1H), 8.37 (s, 1H), 8.14 (d, J = 1.1 Hz, 1H), 7.55–7.40 (m, 1H), 6.90 (bt, J = 5.3 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.97–4.81 (m, 1H), 4.18 (d, J = 14.5 Hz, 0.5H), 3.77 (d, J = 14.5 Hz, 0.5H), 3.73-3.50 (m, 3H), 3.28–3.17 (m, 3H), 2.86-2.76 (m, 0.5H), 2.72-2.59 (m, 0.5H), 2.45–2.29 (m, 1.5H), 1.86 (dd, J = 11.4, 10.3 Hz, 0.5H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 1.10-0.95 (m, 6H).
72	**548.06**	(DMSO-d_6) δ 9.32 (s, 2H), 8.80 – 8.75 (m, 1H), 8.44 (brs, 1H), 8.34 (d, J = 1.6 Hz, 1H), 8.13 (d, J = 1.5 Hz, 1H), 7.48 (d, J = 5.1 Hz, 1H), 7.08 (t, J = 5.1 Hz, 1H), 4.89 (q, J = 6.6 Hz, 1H), 4.13 (d, J = 14.1 Hz, 1H), 3.83 (d, J = 14.2 Hz, 1H), 3.28 – 3.20 (m, 5H), 3.11 – 2.98 (m, 2H), 2.14 (ddd, J = 16.5, 12.3, 8.2 Hz, 2H), 1.97 – 1.85 (m, 2H), 1.85 – 1.74 (m, 3H), 1.13 (dd, J = 9.4, 5.0 Hz, 3H).
73	**532.15**	(DMSO-d_6) δ 10.63 (s, 1H), 9.34 (s, 2H), 8.75 (d, J = 5.5 Hz, 1H), 8.49 – 8.27 (m, 2H), 8.14 (d, J = 1.5 Hz, 1H), 7.36 (d, J = 5.5 Hz, 1H), 6.88 (t, J = 5.5 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.99 – 4.83 (m, 1H), 4.64 (s, 4H), 3.68 (s, 2H), 3.41 (s, 4H), 3.23 (dd, J = 7.2, 5.8 Hz, 2H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).
74	**576.19**	(丙酮-d_6) δ 8.79 (s, 2H), 8.75 (dd, J = 5.2, 0.7 Hz, 1H), 8.49 (s, 1H), 8.22 (d, J = 1.6 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.58 (dd, J = 5.2, 1.6 Hz, 1H), 7.17 (s, 1H), 4.50 – 4.42 (m, 2H), 3.44 – 3.32 (m, 4H), 2.20 – 2.12 (m, 2H), 1.62 (s, 6H), 1.53 – 1.44 (m, 2H), 1.29 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H).

[0840]

75	**548.12 [M-H]⁻**	(DMSO-d_6) δ 10.96 (br s, 1H), 10.73 (br s, 1H), 9.32 (s, 2H), 8.68 (d, J= 5.60 Hz, 1H), 8.35 (s, 1H), 8.15 (s, 1H), 7.93 (s, 1H), 7.13 (d, J= 5.60 Hz, 1H), 7.00 (br s, 1H), 4.87 (m, 1H), 4.69 (m, 2H), 3.81 (m, 3H), 3.64 (m, 2H), 3.54-3.57 (m, 2H), 3.19-3.24 (m, 5H), 1.47 (t, J= 6.40 Hz, 3H) 和 1.11 (t, J=7.20 Hz, 3H).
76	**518.09 [M-H]⁻**	(DMSO-d_6) δ 10.62 (br s, 1H), 9.32 (s, 2H), 8.73 (d, J= 4.40 Hz, 1H), 8.37-8.39 (m, 2H), 8.13 (s, 1H), 7.36 (d, J= 4.40 Hz, 1H), 6.85 (m, 1H), 5.30 (d, J= 5.60 Hz, 1H), 4.86-4.91 (m, 1H), 4.02 (m, 1H), 3.76 (br s, 2H), 3.59 (m, 2H), 3.21 (m, 2H), 3.15 (s, 3H), 2.95 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H) 和 1.09 (t, J=7.20 Hz, 3H).
77	**518.11 [M-H]⁻**	(DMSO-d_6) δ 10.63 (br s, 1H), 9.32 (s, 2H), 8.74 (d, J= 4.80 Hz, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.12 (s, 1H), 7.41 (d, J= 4.80 Hz, 1H), 6.88 (m, 1H), 5.30 (d, J=5.20 Hz, 1H), 4.85-4.89 (m, 1H), 4.74 (d, J=4.40 Hz, 1H), 4.22 (m, 1H), 3.68-3.72 (m, 2H), 3.38 (m, 1H), 3.20-3.23 (m, 2H), 2.67-2.72 (m, 2H), 2.38-2.41 (m, 1H), 1.98-2.05 (m, 1H), 1.55-1.61 (m, 1H), 1.47 (d, J= 6.80 Hz, 3H) 和 1.09 (t, J=7.20 Hz, 3H).
78	**509.1**	(DMSO-d_6) δ 10.63 (br s, 1H), 9.21 (s, 2H), 8.61 (s, 1H), 8.26 (d, J= 5.20 Hz, 1H), 8.20 (s, 1H), 7.82 (m, 1H), 6.84 (m, 1H), 6.55 (d, J= 5.60 Hz, 1H), 5.17 (s, 1H), 3.78 (m, 2H), 3.63 (m, 2H), 3.38 (s, 3H), 3.20 (m, 2H), 1.55 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H)
79	**548.19**	(DMSO-d_6 + D_2O): δ 9.32 (s, 2H), 8.68 (s, 1H), 8.56 (d, J= 6.80 Hz, 1H), 8.30 (s, 1H), 7.18 (d, J= 6.80 Hz, 1H), 3.67 (m, 4H), 3.18-3.22 (m, 6H), 2.34 (m, 2H), 1.55 (s, 6H), 1.29 (t, J= 7.20 Hz, 3H) 和 1.09 (t, J= 7.20 Hz, 3H)
80	**509.16**	(DMSO-d_6 + D_2O): δ 9.31 (s, 2H), 8.65 (d, J= 5.20 Hz, 1H), 8.21-8.24 (m, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.23 (m, 1H), 4.36-4.45 (m, 2H), 3.74 (m, 2H), 3.36 (s, 3H), 3.14-3.18 (m, 2H), 1.55 (s, 6H) 和 1.10 (t, J= 7.20 Hz, 3H).
81	**506.12**	(DMSO-d_6) δ 10.63 (bs, 1H), 9.35 (s, 2H), 8.85 (dd, J = 4.8, 0.8 Hz, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.16 (d, J = 1.4 Hz, 1H), 8.04 (td, J = 7.9, 1.8 Hz, 1H), 7.56–7.41 (m, 1H), 6.88 (bs, 1H), 5.33 (d, J = 5.8 Hz, 1H), 4.93 (dd, J = 12.8, 5.7 Hz, 1H), 3.55 (t, J = 4.6 Hz, 4H), 3.29–3.18 (m, 2H), 2.88 (dd, J = 12.6, 5.5 Hz, 1H), 2.79–2.69 (m, 1H), 2.59-2.53 (m, 2H), 2.50–2.42 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H).
82	**421.06**	(DMSO-d_6) δ 10.97 (bs, 1H), 9.34 (s, 2H), 8.85 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 8.08–7.97 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 7.06 (bd, J = 4.3 Hz, 1H), 5.15 (s, 1H), 2.77 (d, J = 4.6 Hz, 3H), 1.59 (s, 6H).
83	**407.07**	(DMSO-d_6) δ 10.75 (bs, 1H), 9.34 (s, 2H), 8.91–8.79 (m, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.15 (s, 1H), 8.09–7.95 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.8 Hz, 1H), 6.80 (d, J = 3.7 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.99–4.78 (m, 1H), 2.78 (d, J = 4.5 Hz, 3H), 1.50 (d, J = 6.6 Hz, 3H).

[0841]

84	**534.13**	(DMSO-d_6) δ 10.66 (br s, 1H), 9.32 (s, 2H), 8.74 (d, J= 4.80 Hz, 1H), 8.43 (br s, 1H), 8.37 (s, 1H), 8.13 (s, 1H), 7.44 (m, 1H), 6.92 (m, 1H), 5.30 (d, J=5.20 Hz, 1H), 4.86 (m, 1H), 4.62 (br s, 1H), 3.76 (br s, 2H), 3.33 (m, 2H), 3.20 (m, 2H), 2.59-2.75 (m, 2H), 1.76 (m, 2H), 1.47 (t, J= 6.40 Hz, 3H), 1.25 (s, 3H) 和 1.09 (t, J=6.80 Hz, 3H).
85	**495.19**	(DMSO-d_6) δ 10.64 (br s, 1H), 9.21 (s, 2H), 8.61 (s, 1H), 8.24 (m, 1H), 8.15 (s, 1H), 7.76 (m, 1H), 6.86 (m, 1H), 6.54 (d, J= 6.0 Hz, 1H), 5.15 (s, 1H), 4.74 (m, 1H), 3.29 (m, 4H), 3.21 (m, 2H), 1.56 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H)
86	**521.26**	(DMSO-d_6) δ 10.62 (br s, 1H), 9.21 (s, 2H), 8.61 (s, 1H), 8.40 (d, J= 6.0 Hz, 1H), 8.19 (s, 1H), 6.91 (br s, 1H), 6.43 (d, J= 6.0 Hz, 1H), 5.84 (s, 1H), 5.15 (s, 1H), 4.10 (br s, 4H), 3.21 (m, 2H), 1.56 (s, 6H), 1.49 (s, 3H) 和 1.12 (t, J= 7.20 Hz, 3H)
87	**575.23 $[M-H]^-$**	(DMSO-d_6) δ 12.54 (br s, 1H), 10.72 (br s, 1H), 9.33 (s, 2H), 8.71 (s, 1H), 8.43 (s, 1H), 8.15 (s, 1H), 7.69 (s, 1H), 6.99 (m, 1H), 5.15 (br s, 1H), 4.26-4.28 (m, 2H), 3.38 (m, 2H), 3.20 (m, 2H), 2.04-2.11 (m, 2H), 1.57 (s, 6H), 1.40-1.45 (m, 2H), 1.22 (s, 3H) 和 1.11 (t, J= 7.20 Hz, 3H)
88	**562.18**	(丙酮-d_6) δ 8.80 (s, 2H), 8.76 (dd, J = 5.0, 0.6 Hz, 1H), 8.40 (s, 1H), 8.22 (d, J = 1.6 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.47 (dd, J = 5.1, 0.9 Hz, 1H), 5.02 (q, J = 6.5 Hz, 1H), 4.50 – 4.42 (m, 2H), 3.43 – 3.33 (m, 4H), 2.19 – 2.13 (m, 2H), 1.54 – 1.44 (m, 5H), 1.29 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H).
89	**560.9**	($CDCl_3$) δ 9.84 (br s, 1H), 9.06 (s, 2H), 8.56 (d, J = 4.2 Hz, 1H), 7.91 (dd, J = 11.7, 4.5 Hz, 2H), 7.83 – 7.67 (m, 2H), 7.55 (d, J = 12.7 Hz, 1H), 7.15 (dd, J = 7.1, 5.0 Hz, 1H), 3.72 (s, 2H), 3.59 – 3.40 (m, 4H), 2.47 (s, 4H), 2.36 (s, 3H), 1.90 (s, 6H), 1.31 (t, J = 7.2 Hz, 3H).
90	**435.16 $[M-H]^-$**	(DMSO-d_6) δ 10.85 (br s, 1H), 10.61 (br s, 1H), 9.30 (s, 2H), 8.50 (m, 1H), 8.34 (s, 1H), 8.09 (s, 1H), 7.80 (s, 1H), 6.87 (m, 2H), 5.31 (d, J= 5.60 Hz, 1H), 4.88 (m, 1H), 3.21 (m, 2H), 1.47 (d, J= 6.40 Hz, 3H) 和 1.11 (t, J= 7.20 Hz, 3H)
91	**564.24**	(DMSO-d_6 + D_2O): δ 9.25 (s, 2H), 8.55 (s, 1H), 8.24 (s, 2H), 6.80 (s, 1H), 4.09 (s, 2H), 3.91 (br s, 2H), 3.76 (br s, 2H), 3.58 (br s, 4H), 3.16-3.24 (m, 4H), 1.54 (s, 6H) 和 1.08 (t, J= 7.20 Hz, 3H)
92	**495.27**	(DMSO-d_6) δ 10.59 (br s, 1H), 9.33 (s, 2H), 8.61 (m, 1H), 8.40 (s, 1H), 8.12 (s, 1H), 8.05 (s, 1H), 7.05 (d, J= 5.20 Hz, 1H), 6.86 (m, 1H), 5.30 (d, J= 5.20 Hz, 1H), 4.87 (m, 1H), 4.36 (m, 2H), 3.73 (m, 2H), 3.33 (s, 3H), 3.21 (m, 2H), 1.49 (d, J= 6.40 Hz, 3H) 和 1.11 (t, J= 7.20 Hz, 3H).

[0842]

93	**507.17**	(DMSO-d_6) δ 10.62 (br s, 1H), 9.20 (s, 2H), 8.60 (s, 1H), 8.42 (d, J= 6.0 Hz, 1H), 8.16 (s, 1H), 6.85 (m, 1H), 6.44 (d, J= 5.60 Hz, 1H), 5.33 (d, J= 5.60 Hz, 1H), 4.86 (t, J= 6.40 Hz, 1H), 4.45 (m, 3H), 4.04 (br s, 2H), 3.30 (s, 3H), 3.22 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H) 和 1.11 (t, J= 7.20 Hz, 3H)
94	**507.27**	(DMSO-d_6) δ 10.65 (br s, 1H), 9.22 (s, 2H), 8.61 (s, 1H), 8.48 (d, J= 6.0 Hz, 1H), 8.16 (s, 1H), 6.85-6.88 (m, 2H), 5.31 (d, J= 5.60 Hz, 1H), 4.88 (m, 1H), 3.75-3.81 (m, 8H), 3.22 (m, 2H), 1.48 (d, J= 6.80 Hz, 3H) 和 1.11 (t, J= 7.20 Hz, 3H)
95	**420.28**	(DMSO-d_6) δ 10.61 (br s, 1H), 8.99 (s, 1H), 8.81 (m, 1H), 8.51 (d, J= 8.0 Hz, 1H), 8.30 (m, 2H), 7.98-8.02 (m, 2H), 7.62 (m, 1H), 7.45 (m, 1H), 6.86 (m, 1H), 5.45 (d, J= 4.40 Hz, 1H), 4.81 (q, J= 5.60 Hz, 1H), 3.21 (m, 2H), 1.43 (d, J= 6.40 Hz, 3H) 和 1.11 (t, J= 7.20 Hz, 3H)
96	**474.2**	(DMSO-d_6) δ 10.63 (br s, 1H), 9.11 (s, 1H), 8.83 (m, 1H), 8.53 (d, J= 8.0 Hz, 1H), 8.42 (m, 1H), 8.35 (s, 1H), 8.07 (s, 1H), 8.0 (m, 1H), 7.75 (d, J= 8.0 Hz, 1H), 7.44 (m, 1H), 7.10 (m, 1H), 6.85 (br s, 1H), 5.22 (m, 1H), 3.21 (m, 2H) 和 1.11 (t, J= 6.8 Hz, 3H)
97	**577.37**	(DMSO-d_6) δ 12.53 (br s, 1H), 10.67 (br s, 1H), 9.23 (s, 2H), 8.62 (s, 1H), 8.42 (br s, 1H), 8.16 (s, 1H), 6.88 (m, 2H), 5.16 (br s, 1H), 4.32 (m, 2H), 3.37 (m, 2H), 3.22 (m, 2H), 2.07-2.11 (m, 2H), 1.56 (s, 6H), 1.44-1.49 (m, 2H), 1.20 (s, 3H) 和 1.12 (t, J= 7.20 Hz, 3H)
98	**463.11**	(DMSO-d_6) δ 10.64 (br s, 1H), 9.37 (s, 2H), 8.83 (br d, J = 3.9 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.16 (s, 1H), 8.02 (td, J = 7.9, 1.8 Hz, 1H), 7.46 (dd, J = 7.1, 5.2 Hz, 1H), 6.85 (t, J = 5.4 Hz, 1H), 4.89 (s, 1H),
99	**576.22**	(丙酮-d_6) δ 8.79 (s, 2H), 8.75 (dd, J = 5.2, 0.7 Hz, 1H), 8.49 (s, 1H), 8.22 (d, J = 1.6 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.58 (dd, J = 5.2, 1.6 Hz, 1H), 4.46 (dt, J = 13.8, 4.2 Hz, 2H), 3.43 – 3.33 (m, 4H), 2.20 – 2.13 (m, 2H), 1.62 (s, 6H), 1.53 – 1.44 (m, 2H), 1.29 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H).
100	**571.08**	(DMSO-d_6) δ 10.62 (s, 1H), 9.39 (s, 2H), 8.92 – 8.76 (m, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.17 (d, J = 1.1 Hz, 1H), 8.04 (td, J = 7.8, 1.8 Hz, 1H), 7.48 (ddd, J = 7.4, 4.9, 0.8 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.30 (s, 1H), 3.84 (td, J = 11.0, 2.2 Hz, 2H), 3.79 – 3.69 (m, 2H), 3.29 – 3.18 (m, 2H), 2.33 – 2.21 (m, 2H), 1.78 (d, J = 12.1 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
101	**535.21**	(DMSO-d_6) δ 11.51 (br s, 1H), 10.96 (br s, 1H), 9.37 (s, 2H), 9.17 (d, J= 4.80 Hz, 1H), 8.97 (s, 1H), 8.30 (s, 1H), 7.74 (d, J= 4.80 Hz, 1H), 7.14 (m, 1H), 4.75 (s, 2H), 4.00 (br s, 4H), 3.62-3.64 (m, 2H), 3.35 (br s, 2H), 3.21 (m, 2H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H).

[0843]

102	**535.22**	(DMSO-d_6 + D_2O): δ 9.77 (s, 1H), 9.34 (s, 2H), 8.88 (s, 1H), 8.53 (s, 1H), 8.21 (s, 1H), 4.68 (s, 2H), 4.03 (br s, 2H), 3.85 (br s, 2H), 3.60 (br s, 2H), 3.49 (br s, 2H), 3.20 (m, 2H), 1.55 (s, 6H) 和 1.09 (t, J= 7.20 Hz, 3H)
103	**523.24**	(DMSO-d_6) δ 10.64 (br s, 1H), 9.21 (s, 2H), 8.62 (s, 1H), 8.24 (d, J= 5.60 Hz, 1H), 8.14 (s, 1H), 7.57 (m, 1H), 6.81 (m, 1H), 6.65 (d, J= 6.0 Hz, 1H), 5.17 (s, 1H), 4.53 (s, 1H), 3.67 (d, J= 5.20 Hz, 1H), 3.36 (m, 1H), 3.20 (m, 2H), 1.55 (s, 6H), 1.23 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H)
104	**521.2**	(DMSO-d_6) δ 10.64 (br s, 1H), 9.33 (s, 2H), 8.60 (d, J= 5.60 Hz, 1H), 8.38 (s, 1H), 8.12 (s, 1H), 8.03 (s, 1H), 7.05 (m, 1H), 6.95 (m, 1H), 4.84-4.89 (m, 1H), 4.18-4.24 (m, 3H), 3.79-3.84 (m, 2H), 3.67-3.73 (m, 1H), 3.19-3.27 (m, 2H), 2.01-2.13 (m, 1H), 1.85-1.93 (m, 2H), 1.70-1.73 (m, 1H), 1.49 (d, J= 6.40 Hz, 3H) 和 1.11 (t, J= 7.20 Hz, 3H).
105	**493.15**	(DMSO-d_6) δ 10.61 (br s, 1H), 9.20 (s, 2H), 8.61 (s, 1H), 8.40 (d, J= 6.0 Hz, 1H), 8.16 (s, 1H), 6.83 (m, 1H), 6.42 (d, J= 6.0 Hz, 1H), 5.90 (d, J= 6.80 Hz, 1H), 5.32 (d, J= 5.60 Hz, 1H), 4.88 (m, 1H), 4.70 (m, 1H), 4.52 (br s, 2H), 4.09 (br s, 2H), 3.21 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H) 和 1.11 (t, J= 7.20 Hz, 3H)
106	**525.22**	(DMSO-d_6) δ 10.67 (br s, 1H), 9.21 (s, 2H), 8.52-8.54 (m, 2H), 8.16 (s, 1H), 6.82 (m, 1H), 5.30 (d, J= 5.60 Hz, 1H), 4.86 (m, 1H), 3.86 (m, 4H), 3.80 (m, 4H), 3.20 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H) 和 1.11 (t, J= 7.20 Hz, 3H)
107	**578.28**	(DMSO-d_6 + D_2O): δ 9.29 (s, 2H), 8.59 (s, 1H), 8.52 (d, J= 6.40 Hz, 1H), 8.22 (s, 1H), 7.06 (d, J= 6.80 Hz, 1H), 3.56-3.79 (m, 8H), 3.37 (m, 2H), 3.33 (s, 3H), 3.21 (m, 2H), 2.50 (m, 2H), 1.54 (s, 6H) 和 1.09 (t, J= 7.20 Hz, 3H)
108	**573.21**	(DMSO-d_6) δ 10.62 (br s, 1H), 9.11 (s, 1H), 8.76 (d, J= 4.80 Hz, 1H), 8.41 (m, 2H), 8.33 (s, 1H), 8.06 (s, 1H), 7.76 (d, J= 8.0 Hz, 1H), 7.44 (m, 1H), 7.10 (m, 1H), 6.85 (m, 1H), 5.22 (m, 1H), 3.64 (s, 2H), 3.61 (m, 4H), 3.21 (m, 2H), 2.43 (m, 4H) 和 1.11 (t, J= 6.8 Hz, 3H)
109	**563.25**	(DMSO-d_6) δ 10.97 (br s, 1H), 9.38 (s, 2H), 8.69 (br s, 1H), 8.41 (s, 1H), 8.14 (s, 1H), 7.66 (br s, 1H), 7.22 (m, 1H), 5.29 (m, 1H), 4.88 (m, 1H), 4.28 (m, 2H), 3.20 (m, 2H), 2.06 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H), 1.33 (m, 2H), 1.22 (m, 2H) 和 1.09-1.12 (m, 6H)
110	**562.22**	(DMSO-d_6) δ 12.29 (br s, 1H), 10.55 (br s, 1H), 9.32 (s, 2H), 8.37 (d, J= 6.0 Hz, 1H), 8.32 (s, 1H), 8.06 (s, 1H), 7.74 (br s, 1H), 6.91 (m, 2H), 5.14 (br s, 1H), 4.08-4.11 (m, 2H), 3.16-3.22 (m, 2H), 3.02-3.07 (m, 2H), 2.55 (m, 1H), 1.91-1.94 (m, 2H), 1.60-1.62 (m, 2H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H)

[0844]

111	**477.09**	(DMSO-d_6) δ 10.62 (s, 1H), 9.39 (s, 2H), 8.92 – 8.76 (m, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.17 (d, J = 1.1 Hz, 1H), 8.04 (td, J = 7.8, 1.8 Hz, 1H), 7.48 (ddd, J = 7.4, 4.9, 0.8 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.30 (s, 1H), 3.84 (td, J = 11.0, 2.2 Hz, 2H), 3.79 – 3.69 (m, 2H), 3.29 – 3.18 (m, 2H), 2.33 – 2.21 (m, 2H), 1.78 (d, J = 12.1 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
112	**560.17**	(DMSO-d_6) δ 10.62 (s, 1H), 9.33 (s, 2H), 8.76 (d, J = 5.0 Hz, 1H), 8.44 – 8.32 (m, 2H), 8.14 (s, 1H), 7.42 (d, J = 4.9 Hz, 1H), 6.88 (t, J = 5.3 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.89 (p, J = 6.5 Hz, 1H), 4.28 (d, J = 5.6 Hz, 4H), 3.60 (s, 2H), 3.24 (dt, J = 14.0, 7.0 Hz, 2H), 2.34 (s, 4H), 1.83 (d, J = 4.9 Hz, 4H), 1.50 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).
113	**449.05**	(DMSO-d_6) δ 10.63 (s, 1H), 9.45 (s, 2H), 8.89 – 8.80 (ddd, J = 4.8, 1.7, 0.6 Hz 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.44 (d, J = 1.4 Hz, 1H), 8.20 (d, J = 1.4 Hz, 1H), 8.04 (td, J = 8.0, 1.7 Hz, 1H), 7.56 – 7.44 (ddd, J = 12.2, 4.8, 0.6 Hz, 1H), 6.87 (t, J = 5.2 Hz, 1H), 6.42 (s, 1H), 5.08 (d, J = 6.7 Hz, 2H), 4.77 (d, J = 6.7 Hz, 2H), 3.28 – 3.20 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H).
114	**546.21 $[M-H]^-$**	(DMSO-d_6) δ 10.61 (br s, 1H), 9.33 (s, 2H), 8.73 (m, 1H), 8.38 (d, J= 6.40 Hz, 2H), 8.13 (s, 1H), 7.37 (m, 1H), 6.85 (m, 1H), 5.15 (s, 1H), 3.75 (s, 2H), 3.18 -3.23 (m, 4H), 3.10 (s, 3H), 3.06 (m, 2H), 1.57 (s, 6H), 1.40 (s, 3H) 和 1.09 (t, J= 7.20 Hz, 3H).
115	**422.2**	(DMSO-d_6) δ 10.74 (br s, 1H), 9.23 (s, 2H), 9.09 (d, J= 4.80 Hz, 2H), 8.71 (s, 1H), 8.23 (s, 1H), 7.57 (t, J= 4.80 Hz, 1H), 6.86 (m, 1H), 5.33 (d, J= 5.60 Hz, 1H), 4.87 (m, 1H), 3.22 (m, 2H), 1.48 (d, J= 6.40 Hz, 3H) 和 1.12 (t, J= 7.20 Hz, 3H)
116	**603.3**	(DMSO-d_6) δ 10.64 (br s, 1H), 9.11 (s, 1H), 8.74 (d, J= 4.0 Hz, 1H), 8.42 (m, 2H), 8.38 (s, 1H), 8.06 (m, 1H), 7.76 (d, J= 7.6 Hz, 1H), 7.36 (m, 1H), 7.12 (m, 1H), 6.86 (m, 1H), 5.22 (m, 1H), 4.02 (m, 1H), 3.76 (s, 2H), 3.58 (br s, 2H), 3.21 (m, 2H), 3.15 (s, 3H), 2.95 (br s, 2H) 和 1.11 (t, J= 7.20 Hz, 3H)
117	**563.31**	(DMSO-d_6) δ 12.70 (br s, 1H), 10.92 (br s, 1H), 9.35 (s, 2H), 8.72 (br s, 1H), 8.45 (m, 1H), 8.35 (s, 1H), 7.12 (m, 1H), 7.02 (m, 1H), 4.88 (m, 1H), 3.54 (m, 2H), 3.22 (m, 2H), 2.53 (m, 3H), 2.20 (m, 2H), 1.57 (m, 2H), 1.49 (d, J= 6.40 Hz, 3H), 1.24 (s, 3H) 和 1.12 (t, J= 7.20 Hz, 3H)
118	**451.1**	(DMSO-d_6) δ 10.62 (s, 1H), 9.33 (s, 2H), 8.83 (d, J = 4.2 Hz, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.39 (s, 1H), 8.14 (s, 1H), 8.02 (t, J = 7.6 Hz, 1H), 7.54 – 7.40 (m, 1H), 6.80 (d, J = 54.2 Hz, 1H), 5.06 (d, J = 6.5 Hz, 1H), 4.54 (d, J = 5.6 Hz, 1H), 4.49 (t, J = 5.7 Hz, 1H), 4.09 (dd, J = 11.5, 5.6 Hz, 1H), 3.28 – 3.16 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H), 1.07 (d, J = 6.3 Hz, 3H).
119	**461.12**	(DMSO-d_6) δ 10.61 (s, 1H), 9.32 (s, 2H), 8.83 (d, J = 4.1 Hz, 1H), 8.52 (d, J = 8.2 Hz, 1H), 8.39 (d, J = 1.4 Hz, 1H), 8.14 (s, 1H), 8.02 (td, J = 7.9, 1.7 Hz, 1H), 7.46 (dd, J = 7.2, 5.1 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.08 (s, 1H), 3.26

[0845]

120	**535.22**	(DMSO-d_6) δ 10.72 (br s, 1H), 9.24 (s, 2H), 8.99 (s, 2H), 8.69 (s, 1H), 8.22 (s, 1H), 6.83 (m, 1H), 5.16 (s, 1H), 3.60-3.63 (m, 6H), 3.22 (m, 2H), 2.44 (br s, 4H), 1.56 (s, 6H) 和 1.10 (t, J= 7.20 Hz, 3H).
121	**520.13**	(DMSO-d_6) δ 10.62 (s, 1H), 9.32 (s, 2H), 8.76 (d, J = 5.2 Hz, 1H), 8.42 (s, 1H), 8.36 (d, J = 1.6 Hz, 1H), 8.12 (d, J = 1.4 Hz, 1H), 7.44 (dd, J = 5.1, 1.0 Hz, 1H), 6.89 (t, J = 5.3 Hz, 1H), 5.28 (d, J = 5.6 Hz, 1H), 4.94 – 4.82 (m, 1H), 3.65 (s, 2H), 3.64 – 3.58 (m, 4H), 3.29 – 3.14 (m, 2H), 2.47 – 2.41 (m, 4H), 1.49 (d, J = 6.6 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).
122	**520.13**	(DMSO-d_6) δ 10.64 (s, 1H), 9.32 (s, 2H), 8.76 (d, J = 4.9 Hz, 1H), 8.42 (s, 1H), 8.36 (d, J = 1.6 Hz, 1H), 8.12 (d, J = 1.5 Hz, 1H), 7.44 (dd, J = 5.1, 1.0 Hz, 1H), 6.92 (s, 1H), 5.28 (d, J = 5.6 Hz, 1H), 4.88 (p, J = 6.5 Hz, 1H), 3.65 (s, 2H), 3.64 – 3.59 (m, 4H), 3.21 (dt, J = 12.8, 6.5 Hz, 2H), 2.47 – 2.40 (m, 4H), 1.49 (d, J = 6.6 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).
123	**549.09**	(DMSO-d_6) δ 10.67 (s, 1H), 9.43 (s, 2H), 8.85 (dd, J = 5.0, 0.9 Hz, 1H), 8.56 (d, J = 8.1 Hz, 1H), 8.44 (d, J = 1.4 Hz, 1H), 8.19 (d, J = 1.4 Hz, 1H), 8.04 (td, J = 8.1, 1.8 Hz, 1H), 7.48 (dd, J = 7.0, 5.0 Hz, 1H), 6.88 (s, 1H), 5.14 (d, J = 7.4 Hz, 2H), 4.93 (d, J = 7.4 Hz, 2H), 3.24 (m, 2H), 2.75 (t, J = 6.7 Hz, 2H), 2.57 (t, J = 6.7 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
124	**551.12**	(DMSO-d_6) δ 12.18 (s, 1H), 10.64 (s, 1H), 9.38 (s, 2H), 8.85 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 8.43 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H), 8.10 – 7.97 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.88 (t, J = 5.2 Hz, 1H), 5.47 (s, 1H), 4.50 (d, J = 10.6 Hz, 1H), 4.37 (d, J = 10.6 Hz, 1H), 3.23 (m, 2H), 2.50 – 2.38 (m, 4H), 1.58 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H).
125	**576.18**	(DMSO-d_6) δ 10.60 (s, 1H), 9.39 (s, 2H), 8.78 (d, J = 4.9 Hz, 1H), 8.45 (s, 1H), 8.41 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.46 (dd, J = 5.1, 1.0 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.30 (s, 1H), 3.84 (td, J = 11.0, 2.2 Hz, 2H), 3.77 – 3.70 (m, 2H), 3.66 (s, 2H), 3.65 – 3.60 (m, 4H), 3.24 (dd, J = 7.1, 5.8 Hz, 2H), 2.49 – 2.41 (m, 4H), 2.29 (td, J = 13.6, 4.8 Hz, 2H), 1.79 (d, J = 12.2 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
126	**478.02**	(DMSO-d_6) δ 9.38 (s, 2H), 8.84 (d, J = 3.7 Hz, 1H), 8.59 – 8.43 (m, 4H), 8.39 (s, 1H), 8.16 (s, 1H), 8.04 (t, J = 7.4 Hz, 1H), 7.54 – 7.42 (m, 1H), 7.34 (brs, 1H), 6.08 – 5.92 (m, 1H), 4.01 – 3.86 (m, 2H), 3.27 – 3.18 (m, 2H), 1.70 (d, J = 6.6 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H).
127	**493.11**	(DMSO-d_6) δ 10.62 (s, 1H), 9.37 (s, 2H), 8.83 (d, J = 4.0 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.15 (br s, 1H), 8.02 (td, J = 7.9, 1.8 Hz, 1H), 7.47 (dd, J = 7.1, 5.2 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.23 (s, 1H), 3.28 – 3.18 (m, 2H), 3.14 – 2.97 (m, 2H), 2.55 – 2.51 (m, 2H), 2.36 – 2.25 (m, 2H), 2.09 – 1.99 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H).

[0846]

128	**490.1**	(DMSO-d_6) δ 10.71 (br s, 1H), 9.38 (s, 2H), 8.87 – 8.83 (m, 1H), 8.55 (m, J = 8.4 Hz, 1H), 8.42 (d, J = 1.6 Hz, 1H), 8.23 (br s, 1H), 8.17 (d, J = 1.6 Hz, 1H), 8.06 – 8.01 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.96 (t, J = 5.5 Hz, 1H), 5.21 (s, 1H), 3.28 – 3.16 (m, 4H), 2.71 – 2.61 (m, 2H), 2.36 – 2.23 (m, 5H), 1.83 (br d, J = 12.3 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
129	**535.11**	(DMSO-d_6) δ 10.80 (br s, 1H), 9.60 (br s, 2H), 9.36 (s, 2H), 8.85 (d, J = 4.7 Hz, 1H), 8.54 (d, J = 7.8 Hz, 1H), 8.40 (s, 1H), 8.26 (br s, 3H), 8.16 (s, 1H), 8.04 (t, J = 7.8 Hz, 1H), 7.49 (dd, J = 7.0, 4.7 Hz, 1H), 7.11 (br s, 1H), 4.19 (s, 2H), 3.29 – 3.16 (m, 6H), 1.87 (s, 6H), 1.13 (t, J = 7.1 Hz, 3H).
130	**487.1**	($CDCl_3$) δ 8.98 (s, 2H), 8.63 (d, J = 23.2 Hz, 1H), 8.01 – 7.64 (m, 4H), 7.24 – 7.19 (m, 1H), 6.14 – 5.66 (m, 1H), 4.92 (d, J = 55.8 Hz, 1H), 4.29 – 4.10 (m, 1H), 3.29 – 3.23 (m, 2H), 1.11 (t, J = 6.7 Hz, 3H).
131	**505.1**	($CDCl_3$) δ 9.08 (s, 2H), 8.78 (d, J = 4.4 Hz, 1H), 8.07 – 7.76 (m, 4H), 7.34 – 7.27 (m, 1H), 5.20 (s, 1H), 4.67 (d, J = 7.1 Hz, 1H), 3.48 – 3.36 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H).
132	**505.88**	(DMSO-d_6) δ 10.81 (bs, 1H), 9.37 (s, 2H), 8.84 (d, J = 4.1 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.47–8.29 (m, 4H), 8.16 (d, J = 1.3 Hz, 1H), 8.04 (t, J = 7.7 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.11 (bs, 1H), 4.25–4.06 (m, 1H), 3.29–3.13 (m, 2H), 1.91 (s, 3H), 1.81 (s, 3H), 1.54 (d, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H).
133	**521.09**	(DMSO-d_6) δ 10.75 (s, 1H), 9.33 (s, 2H), 8.86 – 8.79 (m, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.6 Hz, 1H), 8.06 – 7.97 (m, 1H), 7.50 – 7.42 (m, 1H), 6.99 (s, 1H), 5.85 (q, J = 6.7 Hz, 1H), 3.22 (dd, J = 7.1, 5.7 Hz, 2H), 2.69 – 2.59 (m, 2H), 2.55 (dd, J = 13.1, 6.8 Hz, 2H), 1.61 (d, J = 6.8 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).
134	**521.1**	(DMSO-d_6) δ 10.80 (s, 1H), 9.33 (s, 2H), 8.82 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.6 Hz, 1H), 8.06 – 7.97 (m, 1H), 7.50 – 7.42 (m, 1H), 7.03 (s, 1H), 5.85 (q, J = 6.7 Hz, 1H), 3.22 (dd, J = 7.1, 5.7 Hz, 2H), 2.67 – 2.59 (m, 2H), 2.47 – 2.40 (m, 2H), 1.61 (d, J = 6.8 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).
135	**550.18**	(DMSO-d_6) δ 10.62 (s, 1H), 9.35 (s, 2H), 8.78 (d, J = 4.8 Hz, 1H), 8.44 (s, 1H), 8.39 (s, 1H), 8.15 (s, 1H), 7.45 (d, J = 4.8 Hz, 1H), 6.88 (m, 1H), 5.04 (s, 1H), 4.68 (t, J = 6.0 Hz, 1H), 3.82 – 3.70 (m, 2H), 3.66 (s, 2H), 3.63 (s, 4H), 3.24 (dd, J = 12.9, 6.8 Hz, 2H), 2.45 (s, 4H), 1.52 (s, 3H), 1.14 (t, J = 6.8 Hz, 3H).
136	**506.06**	(DMSO-d_6) δ 9.39 (s, 2H), 8.84 (d, J = 4.1 Hz, 1H), 8.69 (s, 3H), 8.54 (d, J = 8.1 Hz, 1H), 8.40 (d, J = 1.2 Hz, 1H), 8.17 (d, J = 1.3 Hz, 1H), 8.04 (t, J = 7.2 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.21 (s, 1H), 5.95 (q, J = 6.7 Hz, 1H), 3.28 – 3.17 (m, 2H), 1.70 (d, J = 6.7 Hz, 3H), 1.62 (s, 6H), 1.13 (t, J = 7.2 Hz, 3H).

[0847]

137	**492.05**	(DMSO-d_6) δ 9.39 (s, 2H), 8.84 (d, J = 4.1 Hz, 1H), 8.69 (s, 3H), 8.54 (d, J = 8.1 Hz, 1H), 8.40 (d, J = 1.2 Hz, 1H), 8.17 (d, J = 1.3 Hz, 1H), 8.04 (t, J = 7.2 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.21 (s, 1H), 5.95 (q, J = 6.7 Hz, 1H), 3.28 – 3.17 (m, 2H), 1.70 (d, J = 6.7 Hz, 3H), 1.62 (s, 6H), 1.13 (t, J = 7.2 Hz, 3H).
138	**576.2**	(DMSO-d_6) δ 10.61 (s, 1H), 9.36 (s, 2H), 8.84 – 8.81 (m, 1H), 8.52 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.4 Hz, 1H), 8.04 – 7.99 (m, 1H), 7.48 – 7.44 (m, 1H), 6.87 (t, J = 5.4 Hz, 1H), 5.32 (s, 1H), 3.79 (d, J = 12.6 Hz, 2H), 3.30 – 3.18 (m, 4H), 2.10 (td, J = 13.0, 4.4 Hz, 2H), 1.79 (d, J = 12.7 Hz, 2H), 1.43 (s, 9H), 1.12 (t, J = 7.2 Hz, 3H).
139	**509.1**	(DMSO-d_6) δ 10.62 (br s, 1H), 9.38 (s, 2H), 8.85 – 8.81 (m, 1H), 8.52 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.15 (d, J = 1.5 Hz, 1H), 8.04 – 7.99 (m, 1H), 7.46 (ddd, J = 7.5, 4.9, 0.8 Hz, 1H), 6.92 – 6.86 (m, 1H), 5.60 (s, 1H), 3.27 – 3.18 (m, 2H), 3.03 – 2.94 (m, 4H), 2.48 – 2.41 (m, 2H), 2.35 – 2.23 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H).
140	**520.07**	(DMSO-d_6) δ 10.63 (s, 1H), 9.33 (s, 2H), 8.84 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.56 (d, J = 8.4 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.03 (dt, J = 7.6, 1.8 Hz 1H), 7.48 (ddd, J = 7.6, 4.9, 0.9 Hz, 1H), 6.87 (t, J = 5.4 Hz, 1H), 3.27 – 3.20 (m, 2H), 3.18 (s, 2H), 2.27 (s, 6H), 1.80 (s, 6H), 1.14 (t, J = 7.2 Hz, 3H).
141	**562.13**	(DMSO-d_6) δ 10.63 (s, 1H), 9.33 (s, 2H), 8.84 (ddd, J = 4.9, 1.7, 0.8 Hz, 1H), 8.56 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.03 (td, J = 7.7, 1.7 Hz, 1H), 7.48 (ddd, J = 7.7, 4.9, 0.8 Hz, 1H), 6.86 (t, J = 5.4 Hz, 1H), 3.61 – 3.54 (m, 4H), 3.25 (s, 2H), 3.23 (m, 2H), 2.54 (m, 4H), 1.80 (s, 6H), 1.14 (t, J = 7.2 Hz, 3H).
142	**548.29**	(DMSO-d_6) δ 10.60 (s, 1H) 9.32 (s, 2H), 8.75 (d, J = 5.2 Hz, 1H), 8.41 (s, 1H), 8.38 (d, J = 1.2 Hz, 1H), 8.12 (s, 1H), 7.42 (d, J = 5.2 Hz, 1H), 6.90 (t, J = 5.2 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.88 (p, J = 6.4 Hz, 1H), 3.61 (m, 4H), 3.22 (m, 2H), 2.72 (d, J = 10.8 Hz, 2H), 1.73 (t, J = 10.8 Hz, 2H), 1.48 (d, J = 6.4 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.4 Hz, 6H).
143	**548.27**	(DMSO-d_6) δ 10.60 (s, 1H) 9.32 (s, 2H), 8.75 (d, J = 5.2 Hz, 1H), 8.41 (s, 1H), 8.38 (d, J = 1.2 Hz, 1H), 8.12 (s, 1H), 7.42 (d, J = 5.2 Hz, 1H), 6.90 (t, J = 5.2 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.88 (p, J = 6.4 Hz, 1H), 3.61 (m, 4H), 3.22 (m, 2H), 2.72 (d, J = 10.8 Hz, 2H), 1.73 (t, J = 10.8 Hz, 2H), 1.48 (d, J = 6.4 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.4 Hz, 6H).
144	**534**	(DMSO-d_6) δ 10.86 (bs, 1H), 9.33 (s, 2H), 8.91–8.78 (m, 1H), 8.57 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 8.10–7.99 (m, 1H), 7.91 (s, 2H), 7.56–7.42 (m, 1H), 7.17 (bs, 1H), 3.32–3.14 (m, 2H), 2.80 (dd, J = 12.8, 6.5 Hz, 2H), 2.39 (t, J = 6.7 Hz, 2H), 1.79 (s, 6H), 1.69–1.50 (m, 4H), 1.14 (t, J = 7.2 Hz, 3H).

[0848]

145	**562.18**	(DMSO-d_6) δ 10.83 (bs, 1H), 10.22 (bs, 1H), 9.34 (s, 2H), 8.85 (d, J = 4.0 Hz, 1H), 8.57 (d, J = 8.2 Hz, 1H), 8.41 (d, J = 1.5 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.09–7.97 (m, 1H), 7.49 (dd, J = 7.2, 5.0 Hz, 1H), 7.15 (bs, 1H), 3.22 (dd, J = 12.3, 6.9 Hz, 2H), 3.11 – 2.97 (m, 2H), 2.74 (d, J = 4.9 Hz, 6H), 2.41 (t, J = 7.1 Hz, 2H), 1.79 (s, 6H), 1.77–1.67 (m, 2H), 1.64–1.48 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H).
146	**492.07**	(DMSO-d_6) δ 10.87 (bs, 1H), 9.36 (s, 2H), 8.85 (d, J = 4.2 Hz, 1H), 8.54 (d, J = 8.1 Hz, 1H), 8.39 (d, J = 1.3 Hz, 1H), 8.33 (s, 2H), 8.16 (d, J = 1.3 Hz, 1H), 8.04 (t, J = 7.2 Hz, 1H), 7.49 (dd, J = 7.1, 5.0 Hz, 1H), 7.21 (bs, 1H), 3.89 (d, J = 5.5 Hz, 2H), 3.32–3.11 (m, 2H), 1.86 (s, 6H), 1.13 (t, J = 7.1 Hz, 3H).
147	**540.22**	(DMSO-d_6) δ 10.63 (br s, 1H), 9.33 (s, 2H), 8.76 (d, J= 4.40 Hz, 1H), 8.38-8.41 (m, 2H), 8.13 (s, 1H), 7.40 (m, 1H), 6.86 (m, 1H), 5.16 (s, 1H), 3.89 (s, 2H), 3.69-3.76 (m, 4H), 3.21 (m, 2H), 1.57 (s, 6H) 和 1.09 (t, J= 7.20 Hz, 3H)
148	**576.18**	(DMSO-d_6) δ 10.63 (s, 1H), 9.44 (s, 2H), 8.78 (d, J = 5.0 Hz, 1H), 8.48 – 8.37 (m, 2H), 8.19 (d, J = 1.0 Hz, 1H), 7.45 (dd, J = 5.0, 1.0 Hz, 1H), 6.88 (t, J = 5.4 Hz, 1H), 6.42 (s, 1H), 5.08 (d, J = 6.7 Hz, 2H), 4.78 (d, J = 6.7 Hz, 2H), 3.69 – 3.59 (m, 4H), 3.29 – 3.18 (m, 2H), 2.75 (d, J = 10.5 Hz, 2H), 1.76 (t, J = 10.5 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.3 Hz, 6H).
149[a]	498.97 **[M-H]⁻**	(DMSO-d_6) δ 9.08 (s, 2H), 8.61 (d, *J* = 4.2 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.86 (s, 1H), 7.82 (s, 1H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.49 (s, 1H), 7.21 (dd, *J* = 7.0, 5.1 Hz, 1H), 5.35 – 5.19 (m, 1H), 3.14 (dd, *J* = 13.2, 6.9 Hz, 2H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H).
154	548.18	(DMSO-d_6): δ 10.62 (s, 1H), 9.44 (s, 2H), 8.78 (d, J = 5.0 Hz, 1H), 8.55 – 8.33 (m, 2H), 8.19 (d, J = 1.1 Hz, 1H), 7.46 (d, J = 5.0 Hz, 1H), 6.88 (t, J = 5.5 Hz, 1H), 6.42 (s, 1H), 5.08 (d, J = 6.7 Hz, 2H), 4.78 (d, J = 6.7 Hz, 2H), 3.67 (s, 2H), 3.64 (t, J = 4.5 Hz, 4H), 3.28 – 3.19 (m, 2H), 2.48 – 2.42 (m, 4H), 1.14 (t, J = 7.2 Hz, 3H).
155	573.26	(DMSO-d_6): δ 10.64 (br s, 1H), 9.11 (s, 1H), 8.74 (d, J= 4.0 Hz, 1H), 8.42 (m, 2H), 8.38 (s, 1H), 8.06 (m, 1H), 7.76 (d, J= 7.6 Hz, 1H), 7.36 (m, 1H), 7.12 (m, 1H), 6.86 (m, 1H), 5.22 (m, 1H), 4.02 (m, 1H), 3.76 (s, 2H), 3.58 (br s, 2H), 3.21 (m, 2H), 3.15 (s, 3H), 2.95 (br s, 2H) 和 1.11 (t, J= 7.20 Hz, 3H)
156	568.28	(DMSO-d_6): δ 10.62 (br s, 1H), 9.33 (s, 2H), 8.77 (d, J= 4.80 Hz, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 8.13 (s, 1H), 7.45 (d, J= 4.80 Hz, 1H), 6.85 (m, 1H), 5.15 (s, 1H), 3.72 (s, 2H), 3.21 (m, 2H), 2.56 (m, 4H), 2.04 (m, 4H), 1.57 (s, 6H) 和 1.11 (t, J= 7.2 Hz, 3H)

[0849]

157	451.09	(DMSO-d_6): δ 10.62 (s, 1H), 9.36 (s, 2H), 8.91 – 8.78 (m, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 1.4 Hz, 1H), 8.16 (d, J = 1.4 Hz, 1H), 8.09 – 7.97 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.8 Hz, 1H), 6.88 (t, J = 5.3 Hz, 1H), 5.04 (s, 1H), 4.66 (t, J = 6.1 Hz, 1H), 3.81 – 3.66 (m, 2H), 3.29 – 3.17 (m, 2H), 1.52 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H).
158	435.17	(DMSO-d_6): δ 10.64 (br s, 1H), 9.31 (s, 2H), 8.65 (s, 1H), 8.43 (d, J= 8.40 Hz, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.84 (d, J= 8.0 Hz, 1H), 6.90 (m, 1H), 5.31 (d, J= 5.60 Hz, 1H), 4.86 (m, 1H), 3.21 (m, 2H), 2.40 (s, 3H), 1.48 (d, J= 6.40 Hz, 3H) 和 1.11 (t, J= 7.20 Hz, 3H)
159	547.31	(DMSO-d_6): δ 10.62 (br s, 1H), 9.33 (s, 2H), 8.75 (d, J= 4.80 Hz, 1H), 8.40 (m, 2H), 8.13 (s, 1H), 7.41 (d, J= 4.8 Hz, 1H), 6.88 (br s, 1H), 5.15 (s, 1H), 3.62 (s, 2H), 3.21 (m, 2H), 2.35-2.50 (m, 8H), 2.15 (s, 3H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H)
160	518.22	(DMSO-d_6): δ 10.16 (d, J = 4.8 Hz, 1H), 9.39 (s, 2H), 9.03 (d, J = 4.7 Hz, 1H), 8.85 (d, J = 4.0 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.41 (d, J = 1.5 Hz, 1H), 8.18 (d, J = 1.5 Hz, 1H), 8.04 (td, J = 8.0, 1.6 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.18 (s, 1H), 6.01 (q, J = 6.7 Hz, 1H), 4.61 – 4.44 (m, 1H), 3.37 – 3.17 (m, 4H), 2.45 – 2.28 (m, 1H), 2.18 (dq, J = 14.2, 7.3 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.72 (d, J = 6.7 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H).
161	518.15	(DMSO-d_6): δ 10.16 (d, J = 4.8 Hz, 1H), 9.39 (s, 2H), 9.03 (d, J = 4.7 Hz, 1H), 8.85 (d, J = 4.0 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.41 (d, J = 1.5 Hz, 1H), 8.18 (d, J = 1.5 Hz, 1H), 8.04 (td, J = 8.0, 1.6 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.18 (s, 1H), 6.01 (q, J = 6.7 Hz, 1H), 4.61 – 4.44 (m, 1H), 3.37 – 3.17 (m, 4H), 2.45 – 2.28 (m, 1H), 2.18 (dq, J = 14.2, 7.3 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.72 (d, J = 6.7 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H).
162	548.14	(DMSO-d_6): δ 10.41 (br s, 1H), 9.41 (s, 2H), 8.83 (dd, J = 4.8, 0.9 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.6 Hz, 1H), 8.17 (d, J = 1.4 Hz, 1H), 8.03 (td, J = 7.9, 1.8 Hz, 1H), 7.51 – 7.44 (m, 1H), 6.86 (t, J = 5.3 Hz, 1H), 6.44 (s, 1H), 4.40 (br s, 2H), 4.01 (d, J = 8.3 Hz, 2H), 3.28 – 3.17 (m, 2H), 1.42 (s, 9H), 1.12 (t, J = 7.2 Hz, 3H).
163	448.1	(DMSO-d_6): δ 10.64 (s, 1H), 9.49 (s, 2H), 9.19 (s, 1H), 8.84 (ddd, J = 4.8, 1.7, 0.9 Hz, 2H), 8.53 (d, J = 8.3 Hz, 1H), 8.43 (d, J = 1.6 Hz, 1H), 8.21 (d, J = 1.5 Hz, 1H), 8.08 – 7.99 (m, 1H), 7.48 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.92 (t, J = 5.5 Hz, 1H), 4.64 – 4.52 (m, 2H), 4.23 – 4.11 (m, 2H), 3.29 – 3.14 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H).
164	562.2	(DMSO-d_6): δ 10.63 (bs, 1H), 9.35 (s, 2H), 8.78 (d, J = 4.9 Hz, 1H), 8.43 (s, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.4 Hz, 1H), 7.44 (dd, J = 5.1, 1.0 Hz, 1H), 6.89 (t, J = 5.4 Hz, 1H), 5.15 (s, 1H), 3.76–3.52 (m, 4H), 3.29–3.17 (m, 2H), 2.75 (d, J = 10.2 Hz, 2H), 1.75 (t, J = 10.7 Hz, 2H), 1.59 (s, 6H), 1.14 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.3 Hz, 6H).

[0850]

165	589.05	HCl 盐 (DMSO-d_6): δ 10.84 (bs, 1H), 9.82 (bs, 1H), 9.33 (s, 2H), 9.00 (t, J = 5.8 Hz, 1H), 8.85 (d, J = 4.1 Hz, 1H), 8.55 (d, J = 8.1 Hz, 2H), 8.40 (d, J = 1.3 Hz, 1H), 8.16 (d, J = 1.3 Hz, 1H), 8.04 (t, J = 7.1 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.17 (bs, 1H), 4.24–4.16 (m, 2H), 4.03 (qd, J = 17.8, 5.9 Hz, 2H), 3.22 (dd, J = 17.0, 10.5 Hz, 4H), 2.30 (dd, J = 17.4, 9.5 Hz, 1H), 1.87 (t, J = 7.9 Hz, 2H), 1.81 (d, J = 3.1 Hz, 6H), 1.13 (t, J = 7.2 Hz, 3H).
166	531.92	HCl 盐 (DMSO-d_6): δ 10.87 (bs, 1H), 10.07 (bs, 1H), 9.37 (s, 2H), 8.85 (d, J = 4.1 Hz, 2H), 8.59–8.50 (m, 1H), 8.41 (d, J = 1.0 Hz, 1H), 8.17 (d, J = 1.1 Hz, 1H), 8.04 (t, J = 7.3 Hz, 1H), 7.49 (dd, J = 7.0, 4.8 Hz, 1H), 7.20 (s, 1H), 4.56–4.40 (m, 1H), 3.32–3.13 (m, 4H), 2.45–2.21 (m, 2H), 1.98 (dd, J = 13.1, 6.7 Hz, 2H), 1.92 (s, 3H), 1.81 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H).
167	676.25	(DMSO-d_6): δ 12.35 (s, 1H), 10.70 (s, 1H), 9.44 (s, 2H), 8.78 (d, J = 5.5 Hz, 1H), 8.46 (s, 1H), 8.42 (d, J = 1.4 Hz, 1H), 8.18 (d, J = 1.4 Hz, 1H), 7.45 (d, J = 5.5 Hz, 1H), 6.93 (s, 1H), 5.14 (d, J = 7.5 Hz, 2H), 4.94 (d, J = 7.5 Hz, 2H), 3.68 – 3.59 (m, 4H), 3.27 – 3.19 (m, 2H), 2.74 (m, 4H), 2.57 (m, 2H), 1.76 (t, J = 10.7 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.3 Hz, 6H).
168	465.21	(丙酮) δ 9.26 (s, 2H), 8.85 (d, J = 2.2 Hz, 1H), 8.85 (d, J = 2.2 Hz, 1H), 8.42 (d, J = 8.2 Hz, 1H), 8.35 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 8.01 (dd, J = 8.6, 2.0 Hz, 1H), 7.21 (d, J = 24.2 Hz, 1H), 5.05 (q, J = 6.7 Hz, 1H), 4.96 – 4.89 (m, 1H), 4.53 (s, 1H), 4.38 (d, J = 5.2 Hz, 1H), 1.54 (dd, J = 6.6, 4.4 Hz, 6H), 1.21 (t, J = 7.2 Hz, 3H).
169	605.12	(DMSO-d_6): δ 10.63 (s, 1H), 9.33 (s, 2H), 8.84 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 8.55 (d, J = 7.9 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.14 (d, J = 1.5 Hz, 1H), 8.08 – 7.98 (m, 1H), 7.48 (ddd, J = 7.9, 4.8, 0.8 Hz, 1H), 6.90 (t, J = 5.4 Hz, 1H), 3.56 – 3.52 (m, 4H), 3.39 (s, 2H), 3.28 – 3.20 (m, 2H), 2.63 (t, J = 6.2 Hz, 2H), 2.40 – 2.30 (m, 6H), 1.80 (s, 6H), 1.14 (t, J = 7.2 Hz, 3H).
170	549.95	(DMSO-d_6): δ 10.86 (bs, 1H), 9.61 (bs, 2H), 9.36 (s, 2H), 8.84 (s, 1H), 8.53 (d, J = 7.8 Hz, 1H), 8.40 (s, 1H), 8.16 (s, 1H), 8.04 (t, J = 7.2 Hz, 1H), 7.49 (s, 1H), 7.22 (s, 1H), 3.91 (s, 2H), 3.22 (bs, 2H), 1.86 (s, 6H), 1.13 (t, J = 6.9 Hz, 3H).
171	549.93	HCl 盐 - (DMSO-d_6): δ 10.83 (bs, 1H), 9.33 (s, 2H), 8.84 (s, 1H), 8.53 (d, J = 7.7 Hz, 1H), 8.46 (s, 3H), 8.39 (s, 1H), 8.15 (s, 1H), 8.03 (t, J = 6.9 Hz, 1H), 7.48 (s, 1H), 7.18 (s, 1H), 4.20 (s, 1H), 3.22 (s, 2H), 3.01 (qd, J = 17.5, 5.3 Hz, 2H), 1.81 (d, J = 7.2 Hz, 6H), 1.13 (t, J = 6.1 Hz, 3H).（受水阻碍的 COOH 信号）
172	519.97	HCl 盐 - (DMSO-d_6): δ 10.88 (bs, 1H), 9.34 (s, 2H), 8.85 (dd, J = 4.8, 0.8 Hz, 1H), 8.58 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.07–7.90 (m, 4H), 7.53–7.46 (m, 1H), 7.20 (bs, 1H), 3.23 (dd, J = 6.8, 4.9 Hz, 2H), 2.87 (dd, J = 14.8, 6.0 Hz, 2H), 2.48 (d, J = 7.4 Hz, 2H), 1.86–1.79 (m, 8H), 1.14 (t, J = 7.2 Hz, 3H).

[0851]

173	525.15	(DMSO-d_6): δ 10.62 (br s, 1H), 9.40 (s, 2H), 8.86 – 8.80 (m, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 1.5 Hz, 1H), 8.17 (d, J = 1.2 Hz, 1H), 8.02 (td, J = 7.8, 1.8 Hz, 1H), 7.47 (dd, J = 7.1, 5.2 Hz, 1H), 6.91 – 6.81 (m, 1H), 5.81 (s, 1H), 3.43 – 3.33 (m, 2H), 3.26 – 3.17 (m, 2H), 3.17 – 3.05 (m, 2H), 2.64 (t, J = 11.5 Hz, 2H), 2.39 – 2.21 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H)
174	476.07	(DMSO-d_6): δ 10.61 (br s, 1H), 9.41 (s, 2H), 8.85 – 8.82 (m, 1H), 8.54 – 8.50 (m, 2H), 8.41 (d, J = 1.5 Hz, 1H), 8.39 – 8.29 (m, 1H), 8.18 (d, J = 1.5 Hz, 1H), 8.05 – 8.00 (m, 1H), 7.50 – 7.45 (m, 1H), 6.90 – 6.84 (m, 1H), 5.70 (s, 1H), 3.28 – 3.14 (m, 6H), 2.41 – 2.29 (m, 2H), 2.12 – 2.00 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H).
175	548.25	(DMSO-d_6) δ 10.62 (br s, 1H), 9.33 (s, 2H), 8.73 (d, J= 4.40 Hz, 1H), 8.39 (m, 2H), 8.13 (s, 1H), 7.36 (d, J= 4.0 Hz, 1H), 6.86 (m, 1H), 5.16 (s, 1H), 4.08 (m, 1H), 3.74 (s, 2H), 3.58 (m, 2H), 3.35 (m, 2H), 3.19-3.23 (m, 2H), 2.93 (m, 2H), 1.57 (s, 6H) 和 1.06-1.13 (m, 6H)
176	388.14	(DMSO-d_6) δ 10.62 (br s, 1H), 8.95 (s, 2H), 7.73 (s, 1H), 7.69 (s, 1H), 6.68 (m, 1H), 5.09 (s, 1H), 3.84 (s, 3H), 3.15-3.22 (m, 2H), 1.54 (s, 6H) 和 1.09 (t, J= 7.20 Hz, 3H)
177	376.11	(DMSO-d_6) δ 10.80 (br s, 1H), 9.04 (s, 2H), 7.89-8.01 (m, 2H), 6.71 (m, 1H), 5.14 (s, 1H), 3.16-3.22 (m, 2H), 1.54 (s, 6H) 和 1.09 (t, J= 7.20 Hz, 3H)
178	469.08	(DMSO/丙酮) δ 9.20 (s, 2H), 8.54 (d, J = 5.5 Hz, 1H), 8.48 (s, 1H), 8.14 (d, J = 1.6 Hz, 1H), 8.11 (s, 1H), 7.56 – 7.31 (m, 1H), 7.29 (t, J = 4.6 Hz, 1H), 5.30 (s, 1H), 4.90 – 4.81 (m, 1H), 4.02 (s, 3H), 3.24 – 3.14 (m, 2H), 1.47 (d, J = 6.6 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H).
179	563.98	HCl 盐 - (DMSO-d_6): δ 11.03 (s, 1H), 9.36 (s, 2H), 9.34 (s, 2H), 8.85 (d, J = 4.6 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.40 (d, J = 1.3 Hz, 1H), 8.16 (d, J = 1.3 Hz, 1H), 8.05 (dt, J = 8.0, 1.2 Hz, 1H), 7.50 (dd, J = 7.2, 4.6 Hz, 1H), 7.38 (s, 1H), 4.10 (s, 2H), 3.58 (s, 1H), 3.32 – 3.08 (m, 4H), 2.73 (t, J = 7.3 Hz, 2H), 1.86 (s, 6H), 1.13 (t, J = 7.3 Hz, 3H).
180	531.94	HCl 盐 - (DMSO-d_6): δ = 10.85 (bs, 1H), 9.40 (bs, 1H), 9.35 (s, 2H), 9.26 (bs, 1H), 8.85 (d, J = 4.1 Hz, 1H), 8.57 (d, J = 8.2 Hz, 1H), 8.42 (d, J = 1.4 Hz, 1H), 8.17 (d, J = 1.4 Hz, 1H), 8.03 (dd, J = 11.1, 4.4 Hz, 1H), 7.49 (dd, J = 7.1, 4.9 Hz, 1H), 7.15 (bs, 1H), 3.45–3.31 (m, 3H), 3.26-3.14 (m, 4H), 2.24 (q, J = 6.9 Hz, 2H), 1.82 (d, J = 16.6 Hz, 6H), 1.13 (t, J = 7.2 Hz, 3H).
181	547.97	HCl 盐 - (DMSO-d_6): δ 10.87 (bs, 1H), 10.02 (bs, 1H), 9.63 (bs, 1H), 9.39 (s, 2H), 8.85 (d, J = 4.2 Hz, 1H), 8.56 (d, J = 8.2 Hz, 1H), 8.42 (d, J = 1.2 Hz, 1H), 8.18 (d, J = 1.3 Hz, 1H), 8.05 (t, J = 7.7 Hz, 1H), 7.49 (dd, J = 7.1, 5.0 Hz, 1H), 7.19 (bs, 1H), 4.46 (s, 2H), 4.01–3.88 (m, 2H), 3.76 (t, J = 9.8 Hz, 1H), 3.24 (dd, J = 17.6, 11.7 Hz, 3H), 3.15 (bs, 1H), 1.87 (d, J = 32.2 Hz, 6H), 1.13 (t, J = 7.2 Hz, 3H).

[0852]

182	428.19	(DMSO-d_6) δ 10.62 (br s, 1H), 9.02 (s, 2H), 7.69-7.70 (m, 2H), 6.68 (m, 1H), 5.14 (s, 1H), 3.92 (d, J= 6.80 Hz, 2H), 3.14-3.21 (m, 2H), 1.54 (s, 6H), 1.18-1.20 (m, 1H), 1.08 (t, J= 7.20 Hz, 3H), 0.50-0.55 (m, 2H) 和 0.27-0.31 (m, 2H)
183	432.13	(DMSO-d_6) δ 10.63 (br s, 1H), 9.01 (s, 2H), 7.71-7.74 (m, 2H), 6.68 (m, 1H), 5.11 (s, 1H), 4.20 (t, J= 4.80 Hz, 2H), 3.64 (t, J= 4.80 Hz, 2H), 3.24 (s, 3H), 3.16-3.20 (m, 2H), 1.53 (s, 6H), 和 1.09 (t, J= 7.20 Hz, 3H)
184	616	(DMSO-d_6): δ 10.96 (s, 1H), 9.78 – 9.06 (m, 2H), 9.34 (s, 2H), 8.85 (d, J = 4.5 Hz, 1H), 8.55 (d, J = 8.1 Hz, 1H), 8.41 (d, J = 1.4 Hz, 1H), 8.17 (d, J = 1.4 Hz, 1H), 8.05 (td, J = 8.1, 1.7 Hz, 1H), 7.50 (dd, J = 7.1, 4.5 Hz, 1H), 7.26 (s, 1H), 4.12 (s, 4H), 3.58 (s, 2H), 3.32 – 3.15 (m, 4H), 1.87 (s, 6H), 1.13 (t, J = 7.2 Hz, 3H).
185	536.12	(DMSO-d_6): δ 10.69 (s, 1H), 9.33 (s, 2H), 8.77 (d, J = 5.0 Hz, 1H), 8.45 – 8.33 (m, 2H), 8.14 (d, J = 1.4 Hz, 1H), 7.44 (d, J = 5.0 Hz, 1H), 7.02 – 6.89 (m, 1H), 5.30 (s, 1H), 4.90 (d, J = 5.8 Hz, 1H), 3.70 (s, 2H), 3.23 (dd, J = 13.3, 6.5 Hz, 2H), 2.70 (dd, J = 18.3, 6.0 Hz, 8H), 1.51 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).
186	418.2	(DMSO-d_6) δ 10.68 (br s, 1H), 9.06 (s, 2H), 7.71-7.73 (m, 2H), 6.78 (m, 1H), 5.12 (s, 1H), 4.88 (t, J= 5.20 Hz, 1H), 4.12 (t, J= 5.20 Hz, 2H), 3.70 (t, J= 4.80 Hz, 2H), 3.14-3.21 (m, 2H), 1.54 (s, 6H), 和 1.08 (t, J= 7.20 Hz, 3H)
187	550.23	(DMSO-d_6) δ 10.60 (br s, 1H), 9.32 (s, 2H), 8.76 (d, J= 4.80 Hz, 1H), 8.36-8.40 (m, 2H), 8.13 (s, 1H), 7.42 (d, J= 4.40 Hz, 1H), 6.85 (m, 1H), 5.13 (s, 1H), 3.67 (s, 2H), 3.20-3.23 (m, 2H), 2.66-2.69 (m, 8H), 1.57 (s, 6H) 和 1.11 (t, J= 7.20 Hz, 3H)
188	566.23	(DMSO-d_6) δ 10.62 (br s, 1H), 9.32 (s, 2H), 8.78 (d, J= 4.80 Hz, 1H), 8.44 (s, 1H), 8.37 (s, 1H), 8.13 (s, 1H), 7.45 (d, J= 4.80 Hz, 1H), 6.86 (m, 1H), 5.15 (s, 1H), 3.75 (s, 2H), 3.18-3.25 (m, 2H), 2.93 (m, 4H), 2.69-2.79 (m, 4H), 1.57 (s, 6H) 和 1.11 (t, J= 7.60 Hz, 3H)
189	445.22	(DMSO-d_6) δ 10.68 (br s, 1H), 8.98 (s, 2H), 7.83 (s, 1H), 7.58 (s, 1H), 6.70 (m, 1H), 5.11 (br s, 1H), 3.18 (m, 4H), 3.07 (s, 3H), 2.89 (m, 2H), 2.54 (s, 3H), 1.53 (s, 6H), 和 1.08 (t, J= 7.20 Hz, 3H)
190	514.98	(DMSO-d_6) δ 10.60 (br s, 1H), 9.39 (s, 2H), 8.85 (d, J = 4.6 Hz, 1H), 8.61 – 8.49 (m, 1H), 8.47 – 8.38 (m, 1H), 8.22 – 8.15 (m, 1H), 8.04 (t, J = 7.8 Hz, 1H), 7.49 (dd, J = 7.3, 4.9 Hz, 1H), 6.98 – 6.88 (m, 1H), 5.09 (d, J = 7.5 Hz, 2H), 3.25 – 3.21 (m, 2H), 1.88 (s 6H), 1.16 – 1.11 (m, 3H).
191	582.23	(DMSO-d_6 +D_2O) δ 9.25 (s, 2H), 8.74 (d, J= 4.80 Hz, 1H), 8.35 (s, 1H), 8.30 (s, 1H), 8.06 (s, 1H), 7.45 (d, J= 5.20 Hz, 1H), 3.84 (s, 2H), 3.11-3.21 (m, 6H), 2.94 (m, 4H), 1.54 (s, 6H) 和 1.07 (t, J= 7.20 Hz, 3H)

[0853]

192	524.22	(DMSO-d_6) δ 10.64 (br s, 1H), 9.01 (s, 2H), 7.85 (s, 1H), 7.71 (s, 1H), 6.98 (s, 1H), 6.90 (m, 2H), 6.69 (m, 1H), 5.08-5.10 (m, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.17-3.20 (m, 2H), 1.51 (s, 6H), 和 1.09 (t, J= 7.20 Hz, 3H)
193	444.16	(DMSO-d_6) δ 10.62 (br s, 1H), 8.99 (s, 2H), 7.72 (s, 1H), 7.70 (s, 1H), 6.68 (m, 1H), 5.27 (d, J= 5.20 Hz, 1H), 4.82 (m, 1H), 3.99-4.13 (m, 3H), 3.63-3.70 (m, 2H), 3.16-3.20 (m, 2H), 1.90-1.96 (m, 1H), 1.64-1.80 (m, 2H), 1.59-1.64 (m, 1H), 1.46 (d, J= 6.80 Hz, 3H) 和 1.09 (t, J= 7.20 Hz, 3H)
194	429.24	(DMSO-d_6) δ 10.68 (br s, 1H), 9.05 (s, 2H), 7.79 (s, 1H), 7.61 (s, 1H), 6.70 (m, 1H), 5.27 (d, J= 5.60 Hz, 1H), 4.82 (m, 1H), 3.48 (m, 4H), 3.16-3.19 (m, 2H), 2.73 (m, 4H), 1.45 (d, J= 6.40 Hz, 3H) 和 1.08 (t, J= 7.20 Hz, 3H)
195	442.31	(DMSO-d_6) δ 9.11 (s, 2H), 7.69 (m, 1H), 7.30 (s, 1H), 7.05 (m, 1H), 6.57 (m, 1H), 5.14 (s, 1H), 3.19 (m, 5H), 1.98-2.01 (m, 2H), 1.53 (s, 6H), 1.27-1.35 (m, 4H) 和 1.08 (m, 3H)
196	508.09	(DMSO-d_6): δ 9.32 (s, 2H), 8.75 (d, J = 5.0 Hz, 1H), 8.47 (s, 1H), 8.36 (d, J = 1.5 Hz, 1H), 8.20 (s, 1H), 8.13 (d, J = 1.5 Hz, 1H), 7.45 (d, J = 5.0 Hz, 1H), 6.99 (t, J = 5.5 Hz, 1H), 3.94 (s, 3H), 3.53 (t, J = 5.7 Hz, 2H), 3.21 (tt, J = 13.0, 6.5 Hz, 2H), 2.68 (t, J = 5.7 Hz, 2H), 2.54 (s, 1H), 1.57 (s, 6H), 1.12 (t, J = 7.2 Hz, 3H).
197	420	(CD_3OD) δ 8.80 (d, J = 5.2 Hz, 2H), 8.56 (s, 1H), 8.15 - 8.11 (m, 2H), 8.04 (s, 1H), 7.94 - 7.88 (m, 2H), 7.43 (s, 2H), 7.35 (t, J = 7.2 Hz, 1H), 5.03 (q, J = 6.0 Hz, 1H), 3.42 - 3.38 (m, 2H), 1.60 (d, J = 6.4 Hz, 3 H), 1.26 (t, J = 7.2 Hz, 3H).
198	542.3	(DMSO-d_6): δ 10.61 (s, 1H), 9.33 (s, 2H), 8.76 (d, J = 5.2 Hz, 1H), 8.42 (s, 1H), 8.37 (d, J = 1.3 Hz, 1H), 8.13 (d, J = 0.7 Hz, 1H), 7.44 (dd, J = 5.0, 1.1 Hz, 1H), 6.88 (t, J = 5.1 Hz, 1H), 5.75 (s, 1H), 5.13 (s, 1H), 3.64 (s, 2H), 3.26 – 3.17 (m, 2H), 1.57 (s, 6H), 1.12 (t, J = 7.2 Hz, 3H).
199	487.21	(DMSO-d_6) δ 10.63 (br s, 1H), 9.04 (s, 2H), 7.75 (s, 1H), 7.70 (s, 1H), 6.68 (m, 1H), 5.10 (s, 1H), 4.17 (t, J= 5.20 Hz, 2H), 3.53 (m, 4H), 3.15-3.21 (m, 2H), 2.64 (t, J= 5.20 Hz, 2H), 2.37 (m, 4H), 1.53 (s, 6H) 和 1.08 (t, J= 7.20 Hz, 3H)
200	448.14	(DMSO-d_6) δ 10.84 (br s, 1H), 8.93 (s, 2H), 7.63-7.69 (m, 2H), 6.72 (m, 1H), 5.21 (br s, 1H), 3.37 (t, J= 6.40 Hz, 2H), 3.11-3.15 (m, 5H), 2.98 (t, J= 6.40 Hz, 2H), 1.58 (s, 6H), 和 1.04 (t, J= 6.80 Hz, 3H)
201	464.14	(DMSO-d_6) δ 11.06 (br s, 1H), 9.03 (s, 2H), 7.92-7.98 (m, 2H), 6.79 (m, 1H), 5.27 (br s, 1H), 3.65 (m, 1H), 3.45 (m, 1H), 3.02-3.15 (m, 6H), 2.85-2.89 (m, 1H), 1.57 (s, 6H), 和 1.05 (t, J= 7.20 Hz, 3H)

[0854]

202	451.21	(DMSO-d_6): δ 10.59 (s, 1H), 9.33 (s, 2H), 8.63 (d, J = 6 Hz, 1H), 8.38 (d, J = 0.8 Hz, 1H), 8.12 (s, 1H), 8.02 (d, J = 1.2 Hz, 1H), 7.05 (dd, J = 5.6, 2 Hz, 1H), 6.87 (br t, J = 5.2 Hz, 1H), 5.30 (d, J = 5.2 Hz, 1H), 4.88 (p, J = 6 Hz, 1H), 3.99 (s, 3H), 3.21 (p, J = 6.4 Hz, 2H), 1.49 (d, J = 6.4 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).

[0855] [a] 化合物 149 通过在前文所述铃木 (Suzuki) 偶联条件下将前体 81 与中间体 1 偶联的方式制备，随后转化为下述目标化合物。向 1-[5-[2-(乙基氨甲酰基氨基)-7-(2-吡啶基)-1,3- 苯并噻唑 -5- 基] 嘧啶 -2- 基] 乙基二 (2,2,2- 三氯乙基) 磷酸酯 (230mg) 的吡啶 (1.5mL) 和乙酸 (0.3mL) 的混合溶液中加入锌 (177mg) 并将混合物室温搅拌 2h。混合物通过硅藻土过滤，使用吡啶 (3x10mL) 洗涤并真空浓缩。使用 MeOH(30mL) 处理残留物以生成固体，对其通过过滤收集。对其进行反相色谱纯化，依次使用 0-100% ACN/ 水和 50% MeOH/ 水 50%氨洗脱，以得到二铵盐形式的化合物 149(50mg)。

[0856] ADME 试验

[0857] 可使用以下试验评估前药的特性以及前药用于体内递送化合物的潜在适用性。

[0858] 化学稳定性试验

[0859] 可在水溶液中，在四个 pH 值 (即 2.1、4.5、7.4 和 9.1) 下测试化合物的化学稳定性。使用 10%乙腈和来自 DMSO 储液的样品 (2mM) 制备应力溶液 (stress solution)，使得终浓度为 16μM。测试样品使用 C8 反相柱 (Phenomenex Kinetex™2.6μm C8 100 Å LC 柱 50x3mm 或类似) 通过 HPLC 分析，使用 5-100%乙腈 : 水 +0.1%甲酸的洗脱梯度。在 24 小时内使用 2 小时一次的注射进行该试验。使用 254nm 处的峰面积进行数据分析，并使用 LCMS 确定质量。

[0860] 在替代性方法中，稀释溶解在 DMSO 中的化合物，以生成三份 10μM 含 5% DMSO 的 HEPES pH7.4 溶液。将样品在 37℃下孵育 24h 并通过 LCMS 分析，随后加入 2 倍体积的甲醇。通过将峰面积与 T0 样品比较以确定剩余化合物的百分比。

[0861] 测试了代表性化合物 19、123、133 和 134 的化学稳定性，并确定这些化合物在 pH7.4 的条件下是化学稳定的，其 24 小时时残留≥ 95%的化合物。

[0862] 热力学溶解度

[0863] 在 1.5mL EP 管中将约 2mg 的化合物重悬于一定体积的 HEPES 缓冲液 (pH7.4) 中，以制备 5mg/ml 的悬浮液。室温下将试管置于轨道振荡器上然后振荡 24 小时，在台式离心机中以 1400rpm 使得试管离心，以使未溶解的化合物沉淀。取两份 150μL 试样量的上清液，然后转移至两个超速离心管中，20℃下以 357440g 离心 4 小时。随后使用 100μL 甲醇稀释各管中的 50μL 上清液，并通过 HPLC 或 LCMS 分析，通过与标准曲线对比确定溶液中化合物的浓度。测试了代表性化合物 19、123、134 和 153 的热力学溶解度，并确定这些化合物在 pH7.4 的条件下是高度可溶的，溶解度≥ 2mg/mL。

[0864] 微粒体稳定性

[0865] 在 96 孔聚丙烯平板中，制备两份体积 100μl 且浓度为 10μM 的化合物，其中每份含有 100mM KPO_4 缓冲液 pH7.4、5mM $MgCl_2$、25μg/ml 丙甲菌素 (Alamethicin)、1mg/ml (蛋白质) 肝微粒体 (小鼠) 且 DMSO 终浓度为 0.1%。将平板在 37℃预孵育 10 分钟，之后加入 NADPH 和 UDPGA 至终浓度分别为 1mM 和 5mM 以开始反应。将反应在 37℃孵育并在 0、10、30 和

60 分钟时加入 100μl DMSO 终止反应。提取 100μl 的样品并加入 50μl 冰冷的甲醇中并在轨道振荡器上混合 10 分钟以沉淀蛋白质。随后将样品在 10℃下 4000rpm 离心 30 分钟并通过 LCMS 分析上清液。通过由峰值面积进行的线性回归确定 T1/2 和清除率 (clearance)。测试了代表性化合物 19、123、133 和 134 的微粒体稳定性并确定为不稳定，每种情况下主要的代谢物均为母体醇，其半衰期小于 20min。

[0866] 血浆稳定性

[0867] 在 96 孔聚丙烯平板中，对溶解在 DMSO 中的化合物进行稀释，以制备两份体积为 50μl 的试样量的 10μM 溶液，其中清洁的血浆内含 1% DMSO。37℃孵育 5 小时后，向样品中加入 100μl 冰冷的乙腈，并在轨道振荡器上混合 10 分钟以沉淀蛋白质。随后将样品在 10℃下 4000rpm 离心 30 分钟并通过 LCMS 分析上清液。通过将峰面积分别与 DMSO 储液和 T0 样品比较，以确定剩余化合物的回收率和百分比。

[0868] 生物学数据

[0869] 可使用以下方法确定本发明的化合物的体外和体内抗病毒活性。

[0870] 靶标酶试验：测定促旋酶 ATP 酶活性

[0871] 促旋酶将 ATP 转化成 ADP 和无机磷酸盐。所释放的磷酸盐能通过加入孔雀绿溶液检测，并且通过监测 600nm 处的吸光度的增加来进行测量。ATP 酶试验在包含 2mU/μl 促旋酶（金黄色葡萄球菌 (Staphylococcus aureus)A_2B_2 复合物）、0.08mg 双链 DNA、8mM HEPES.KOH pH7.6、100mM 谷氨酸 K、2mM 乙酸镁、2mM DTT、0.01mg BSA 和 5% DMSO 溶液（包含抑制剂）的缓冲液中进行。或者，ATP 酶试验在含有 4.8 促旋酶（来自大肠杆菌 (Escherichia coli) 的 A_2B_2 复合物）、0.08μg/mL ssDNA、35mM Tris pH7.5、24mM KCl、2mM$MgCl_2$、6.5%甘油、2mM DTT、1.8、0.5mg/mL BSA 和 5% DMSO 溶液（含抑制剂）的缓冲液中进行。通过加入 ATP 直到终浓度为 1mM 来开始反应，并且在 30℃孵育 60 分钟。通过加入 200μL 孔雀绿溶液 (0.034%孔雀绿、10mM 钼酸铵、1M HCl、3.4%乙醇、0.01%吐温 20) 停止反应。显色 5 分钟，并且通过分光光度法测量 600nm 处的吸光度。从使用无化合物和无酶的对照样的吸光度读数来测定 IC_{50} 值。

[0872] 本发明的化合物表现出了靶标酶活性，大多数测试的化合物显示出低于 1μg/mL 的促旋酶 ATP 酶活性 IC_{50} 值，其中大多数低于 0.1μg/mL。

[0873] 细菌试验：测定抗菌活性

[0874] 通过液体中或固体培养基上的敏感性试验检测本发明化合物的抗菌活性。通过肉汤微稀释或琼脂稀释法测定针对各株的化合物 MIC，所述方法根据临床实验室标准化研究所指南，临床实验室标准化研究所是原来的国家临床实验室标准委员会（临床实验室标准化研究所，Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically(《用于有氧生长细菌的稀释抗菌敏感性试验的方法》)；认可标准－第 7 版，文献 M7A7。CLSI，Wayne，Pa，2006；临床实验室和标准研究所）。测试的革兰氏阳性菌株包括金黄色葡萄球菌 (Staphylococcus aureus(分离编号 ATCC29213))、表皮葡萄球菌 (Staphylococcus epidermidis(分离编号 ATCC12228))、粪肠球菌 (Enterococcus faecalis(分离编号 ATCC29212))、屎肠球菌 (Enterococcus faecium(分离编号 ATCC700221))、化脓链球菌 (Streptococcus pyogenes(分离编号 ATCC51339)) 和肺炎链球菌 (Streptococcus pneumoniae(分离编号 ATCC49619))。测试的革兰氏阴性菌

株包括流感嗜血杆菌(Haemophilus influenzae(分离编号ATCC49247))、鲍式不动杆菌(Acinetobacter baumannii(分离编号ATCC19606))、大肠杆菌(Escherichia coli(分离编号ATCC25922))、肺炎杆菌(Klebsiella pneumoniae(分离编号ATCC13882))、嗜肺军团菌(Legionella pneumophila(分离编号ATCC33152))、粘膜炎莫拉氏菌(Moraxella catarrhalis(分离编号ATCC 25240))和脑膜炎奈瑟球菌(Neisseria gonorrhoeae(分离编号ATCC49226))。

[0875] 革兰氏阳性抗菌活性

[0876] 测试本发明的代表性化合物针对一种或多种革兰氏阳性菌株的活性,结果示于表1和2。

[0877] 表1. 金黄色葡萄球菌(ATCC29213)最低抑制浓度(MIC)

[0878]

MIC (μg/mL)	代表性化合物示例编号
≤1	1, 2, 3, 4, 6, 7, 8, 10, 12, 13, 14, 15, 17, 18, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 48, 49, 50, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 67, 68, 69, 70, 71, 73, 74, 75, 76, 77, 78, 80, 81, 82, 83, 84, 87, 88, 92, 93, 94, 95, 96, 98,100, 101, 104, 106, 107, 108, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 125, 127, 128, 130, 131, 154, 155, 156, 157, 158, 162, 164, 168, 173, 175, 176, 177, 178, 182, 183, 185, 187, 188, 191, 192, 193, 197, 198, 202
2	16, 20, 45, 52, 65, 66, 79, 85, 91, 99, 103, 109, 110, 150, 151, 159, 196, 199
4	11, 21, 46, 51, 97, 186
8	9, 47, 72, 86, 89, 174

[0879]

16	5, 41, 44, 90, 102, 105, 117, 194

[0880] 表2. 化脓链球菌(ATCC51339)最小抑制浓度(MIC)

[0881]

MIC (μg/mL)	代表性化合物示例编号
≤1	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 45, 48, 49, 50, 51, 52, 53, 54, 55, 56, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 74, 75, 76, 77, 78, 80, 81, 82, 83, 84, 85, 86, 87, 88, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 125, 127, 128, 130, 131, 154, 155, 156, 157, 158, 159, 162, 164, 168, 173, 175, 176, 178, 182, 183, 185, 187, 188, 191, 192, 197
2	13, 57, 79, 89, 90, 151, 174, 177, 186, 193, 199
4	46
8	47, 72, 150, 163
16	41, 44, 102

[0882] 革兰氏阴性抗菌活性

[0883] 也测试了本发明所选的化合物的抗革兰氏阴性菌株流感嗜血杆菌 (ATCC49247) 的活性，结果示于表 3。

[0884] 表 3. 流感嗜血杆菌 (ATCC49247) 最小抑制浓度 (MIC)

[0885]

MIC (μg/mL)	代表性化合物示例编号
≤2	1, 6, 7,8, 10, 15, 17, 22, 23, 27, 28, 30, 31, 32, 35, 36, 38, 39, 40, 43, 53, 55, 56, 58, 59, 61, 62, 63, 64, 68, 69, 70, 71, 73, 74, 75, 76, 80, 81, 82, 83, 87, 88, 92, 95, 96, 99, 100, 104, 111, 113, 114, 115, 116, 118, 119, 121, 122, 125, 127, 130, 131, 154, 155, 157, 158, 168, 173, 175, 178, 185, 187, 198, 202

[0886] 药代动力学试验：测定 PK 曲线

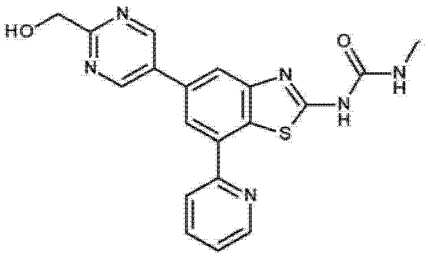
[0887] 化合物的药代动力学曲线是通过如下方法测量的：LC/MS/MS 测量血浆中化合物浓度，随后以单独 1 或 3mg/kg 的剂量或至多 5 种化合物一盒的方式静脉内或经口给予化合物。浓度描述为三种动物的各时间点的平均血浆浓度。通过尾静脉以单个推注剂量的形式给予静脉内剂量制剂。口服剂量制剂通过口服强饲针给予动物。在两种情况下，剂量容量

都是 5.0mL/kg。血液使用颈静脉导管从大鼠中收集，以及通过毛细管导入眼窝窦后丛的方式从麻醉的小鼠中收集。随后对收集的血液进行离心以获得血浆，并且在甲醇中萃取化合物，然后通过 LC/MS/MS 测量化合物浓度。

[0888] 在大鼠试验（IV）中，将所选的本发明的化合物的药代动力学概况与其主要醇类似物（化合物 A 和 B）直接进行比较。

[0889] 1-乙基-3-[5-[2-(羟基甲基)嘧啶-5-基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲（化合物 A）

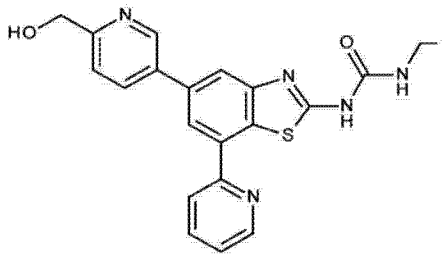
[0890]



MS:406.99 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 9.34 (s, 2H), 8.84 (d, J = 4.1 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.40 (d, J = 1.1 Hz, 1H), 8.16 (s, 1H), 8.03 (td, J = 8.0, 1.6 Hz, 1H), 7.48 (dd, J = 7.0, 5.0 Hz, 1H), 6.91 (s, 1H), 5.39 (t, J = 6.1 Hz, 1H), 4.72 (d, J = 5.9 Hz, 2H), 3.26 – 3.21 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H).

[0891] 1-乙基-3-[5-[6-(羟基甲基)-3-吡啶基]-7-(2-吡啶基)-1,3-苯并噻唑-2-基]脲（化合物 B）

[0892]



MS:406.15 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6):d 10.62 (br s, 1H), 9.0 (d, J= 2.0 Hz, 1H), 8.82 (d, J= 4.40 Hz, 1H), 8.50 (d, J= 8.0 Hz, 1H), 8.30-8.32 (m, 2H), 7.98-8.03 (m, 2H), 7.60 (d, J= 8.40 Hz, 1H), 7.44-7.47 (m, 1H), 6.87 (m, 1H), 5.49 (t, J= 5.60 Hz, 1H), 4.65 (d, J= 5.60 Hz, 2H).

[0893] 结果如表 4 所示，并如图 1A 和 1B 所示，其中 X 轴表示时间（小时）且 Y 轴表示血浆浓度（μg/mL）。下表中提供了 AUC_{iv}、清除率和 $T_{1/2}$ 值，其中 AUC_{iv} 是静脉内（IV）曲线下的面积，$T_{1/2}$ 表示化合物的半衰期。出乎意料的是，与化合物 A 和 B 相比，本发明化合物证实了清除率的提高和 AUC_{iv} 与半衰期的增加。

[0894] 表 4：大鼠试验中所选化合物与其主要醇替代类似化合物 A 和 B 在 AUC_{iv}、清除率和半衰期方面的比较。

[0895]

化合物编号	剂量 (mg/kg)	AUC_{iv} (μg.hr/mL)	清除率 (mL.min/kg)	$T_{1/2}$ (min)
A	3	2	25	81
B	3	1.8	28	60
1	1	3.1	4.3	203
17	3	4	12	107
27	1	1.13	13	158

[0896] 动物感染模型

[0897] 合适的感染模型是本领域技术人员所熟知的并包括下列模型，适用于静脉内（IV）或口服（PO）给药。

[0898] 大腿感染模型

[0899] 小鼠：通过腹膜内给予环磷酰胺（第 4 天 150mg/kg 且第 1 天 100mg/kg）以呈现中性白细胞减少症，在雌性 CD-1 小鼠（18-22g）的大腿上接种约 $2x10^5$cfus 的从新鲜过夜培养物中制备的金黄色葡萄球菌。2 小时后按指示给予化合物并在给药后多个时间点对 cfus 进行计数，方法为获取大腿、在盐水中匀化（冰上操作）和在含活性炭的平板上连续稀释以用于过夜生长和菌落计数。例如，以 30mg/kg 的剂量静脉内给予后，与对照相比，化合物 1 和 17 的菌落形成单位减少了≥ 3log。类似地，以 100mg/kg 的剂量口服给予后，与对照相比，化合物 1 的菌落形成单位减少了≥ 3log。

[0900] 大鼠：通过腹膜内给予环磷酰胺（第 4 和第 1 天 75mg/kg）以呈现中性白细胞减少症，在 SD 大鼠（250-275g）的大腿上接种约 $1x10^7$cfus 的金黄色葡萄球菌 ATCC29213。2 小时后按指示给予化合物并在给药后多个时间点对 cfus 进行计数，方法为获取大腿、在 PBS 中匀化（冰上操作）和在 CLED 琼脂糖平板上连续稀释以用于在 37℃下生长和菌落计数。例如，以≤ 40mg/kg 的剂量静脉内给予后，与对照相比，化合物 1 的菌落形成单位减少了≥ 3log。

[0901] 肺感染模型

[0902] 小鼠（革兰氏阳性）：对麻醉的雌性 CD-1 小鼠（18-22g）经鼻内接种约 10^6cfus 的从新鲜过夜培养物中制备的肺炎链球菌 ATCC6301，接种方法为将 50μl 的接种物放置在鼻孔上并使小鼠吸入。接种后 24 小时按指示给予化合物并在接种后 48 小时时对 cfus 进行计数，方法为获取肺、在 PBS 中匀化（冰上操作）和在 TSA+5％血液平板上连续稀释以用于在 37℃下过夜生长和菌落计数。例如，以≤ 30mg/kg 的剂量静脉内给予后，与对照相比，化合物 1 的菌落形成单位减少了≥ 3log。

[0903] 大鼠（革兰氏阴性）：通过腹膜内给予环磷酰胺以呈现中性白细胞减少症，在麻醉的 SD 大鼠（250-275g）的大腿上经气管接种约 $5x10^7$cfus 的从新鲜培养物中制备的流感嗜血杆菌，接种方法为递送 0.5ml 含接种物的熔融琼脂糖。接种后 5 小时按指示给予化合物随后进行额外的日常处理并在接种后 96 小时时对 cfus 进行计数，方法为获取肺、在 PBS 中匀化（冰上操作）和在细菌生长培养基上连续稀释以确定 cfu。

[0904] 小鼠存活模型：对麻醉的雌性 CD-1 小鼠（18-22g）经鼻内接种约 10^6cfus 的从新

鲜过夜培养物中制备的肺炎链球菌 ATCC6301，接种方法为将 50μl 的接种物放置在鼻孔上并使小鼠吸入。在接种后 24、48 和 72 小时按指示给予化合物并在感染后监测小鼠的存活率，持续监测七或九天。例如，以 10mg/kg 的剂量经静脉给予化合物 1，结果如图 2 所示。化合物 1 表现出改善的疗效，其中 80％的小鼠在第七或第九天存活。作为比较，给予 10mg/kg 利奈唑胺的小鼠在第六天死亡。类似地，以 30mg/kg 的剂量经静脉给予化合物 17 后，90％的小鼠在第七天存活。

[0905] 皮肤感染模型

[0906] 小鼠：通过使用优质的砂板摩擦随后刮削除去皮毛的方式从处死的雌性 CD-1 小鼠（18-22g）的背部表面剥下一片皮肤。通过将 5μl 的接种物（包含约 10^7cfus 的从新鲜过夜培养物中制备的金黄色葡萄球菌）放置在损伤的皮肤上来启动感染。在接种后 4、20、28、44、52、68 和 76 小时按指示给予化合物并在接种后 5 天对 cfus 进行计数，方法为获取损伤的皮肤、在 PBS 中匀化（冰上操作）和在含活性炭的平板上连续稀释以用于生长过夜和菌落计数。

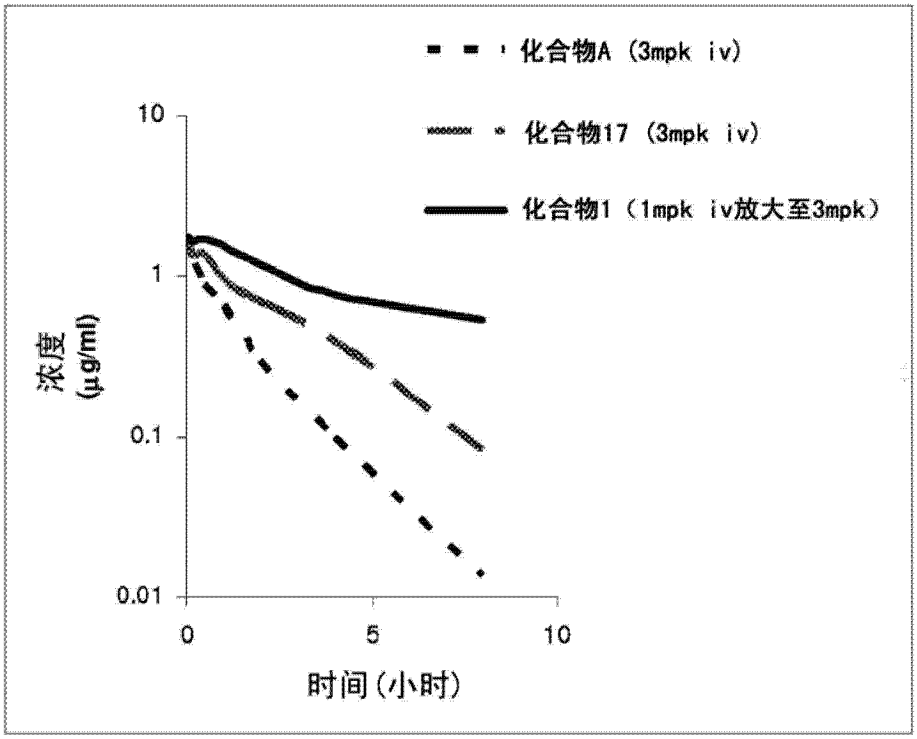
[0907] 败血症感染模型

[0908] 小鼠：使用约 $5x10^5$cfus 的从新鲜过夜培养物中制备并悬浮于 5％猪胃粘蛋白中的金黄色葡萄球菌腹膜内接种雌性 CD-1 小鼠（18-22g）。在接种后 2 小时按指示给予化合物并并在感染后监测小鼠的存活率，持续监测五天。

[0909] 除非另有说明，否则，在本说明书和所附权利要求书中，术语“包括”以及变化形式如“包含”和“含有”应理解为是指包括所述的整数或步骤或者多个整数或步骤的组，但是不排除任何其它整数或步骤或者多个整数或步骤的组。

[0910] 在说明书中对任何在先出版物（或由此得到的资料）或任何已知事物的参考不作为并且不应被看作承认或认可或者以任何形式提示在先出版物（或由此得到的资料）或任何已知事物形成本说明书涉及的领域中公知常识的一部分。

A


化合物A（3mpk iv）
化合物17（3mpk iv）
化合物1（1mpk iv放大至3mpk）
10
1
0.1
0.01
浓度
(μg/ml)
0
5
10
时间(小时)

B

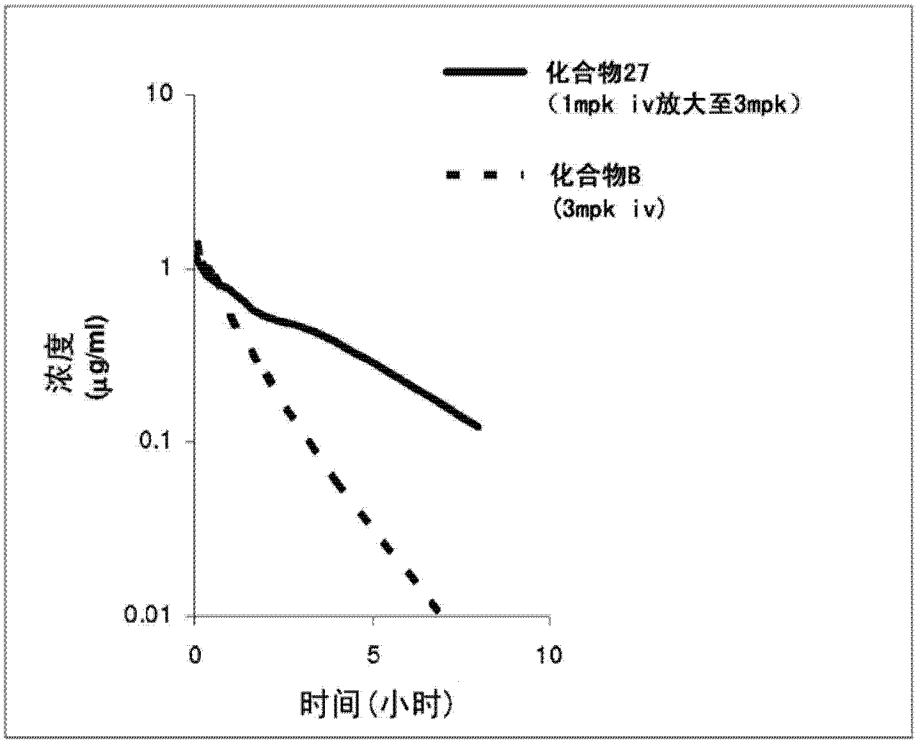

化合物27
（1mpk iv放大至3mpk）
化合物B
（3mpk iv）
10
1
0.1
0.01
浓度
(μg/ml)
0
5
10
时间(小时)

图 1

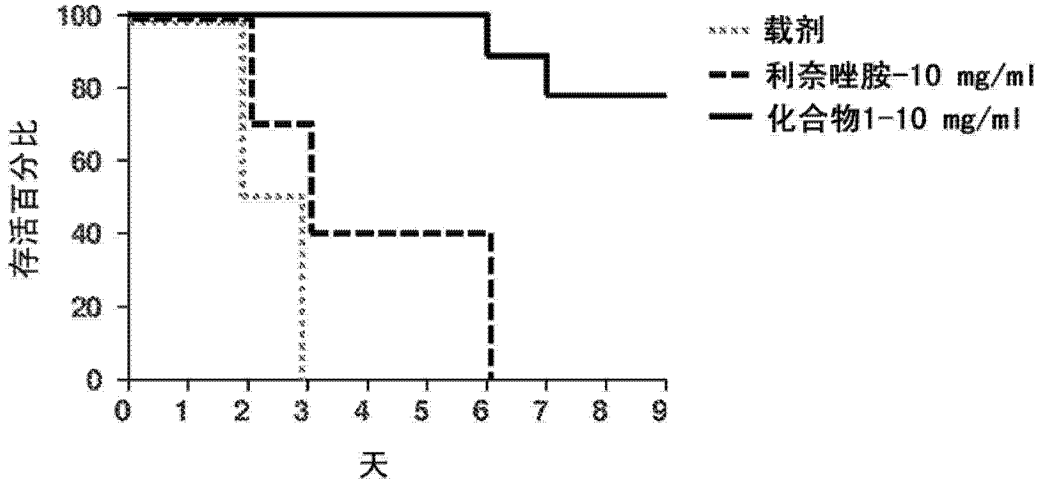

100
80
60
40
20
0
存活百分比
0 1 2 3 4 5 6 7 8 9
天
载剂
利奈唑胺-10 mg/ml
化合物1-10 mg/ml

图 2