

6-BRIDGED HETEROARYLDIHYDROPYRIMIDINES FOR THE TREATMENT AND PROPHYLAXIS OF HEPATITIS B VIRUS INFECTION

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a human, and in particular to Hepatitis B virus (HBV) inhibitors by targeting on HBV capsid for the treatment of HBV infection.

5

FIELD OF THE INVENTION

HBV is a species of the hepadnaviridae family of viruses. HBV is a serious public health problem worldwide, with more than 400 million people especially in Asia-Pacific regions
10 chronically infected by this small enveloped DNA virus. Although most individuals seem to resolve the infection following acute symptoms, 15-40% of HBV patients will finally develop clinical diseases during their lifespan, most notably, hepatitis, liver cirrhosis, and hepatocellular carcinoma. Every year 500,000 to 1 million people die from the end stage of liver diseases caused by HBV infection.

15 HBV lifecycle begins with the binding of the “Dane” particle with an unidentified receptor on the surface of hepatocyte. Following entry, viral genome is delivered into nucleus where a covalently closed circular DNA (cccDNA) is formed through DNA repair of viral relaxed circular DNA. Unlike the mechanisms of most other DNA viruses, HBV cccDNA replicates through the retrotranscription of a 1.1-genome unit-length RNA copy (pregenomic RNA). Viral
20 pregenomic RNA interacts with other two viral components, capsid protein and polymerase, as well as some host factors, to form capsid particles where viral DNA replication occurs. Most copies of the encapsidated genome then efficiently associate with the envelope proteins for virion assembly and secretion; a minority of these genomes is shunted to the nucleus, where they are converted to cccDNA.

25 Currently, there are two types of anti-HBV agents on the market, nucleoside (tide) analogs targeting viral polymerase (lamivudine, adefovir, tenofovir, telbivudine and entecavir) and interferon modulating host immune functions. Mutations in the primary sequence of the polymerase that confer resistance to lamivudine and adefovir have been identified clinically and
Yingxian Zhu / 14.04.2014

underlie a rebound of serum virus titers that 70% of treated patients experience within 3 years of the start of lamivudine therapy. Although resistance to telbivudine, adefovir, and entecavir occurs more rarely, it has been recorded. Interferon alpha is the other major therapy available for hepatitis B, but it is limited by a poor long-term response and debilitating side effects. Some viral genotypes do not show good responses to interferon therapy. Now, the standard of clinic cure of HBV infection is the loss and/or seroconversion of HBsAg. The majority (around or more than 90%) of treated patients fail to achieve this goal. This drawback is mainly due to the presence of a stable pool of viral cccDNA in nucleus that doesn't replicate itself, therefore, shows no accessibility to nucleoside (tide) analogs.

Hence, there is certainly a medical need for treatments with improved characteristics and for a diversity of approaches in the development of therapies for HBV infection.

HBV capsid protein plays essential roles in HBV replication. HBV has an icosahedral core comprising of 240 copies of the capsid (or core) protein. The predominant biological function of capsid protein is to act as a structural protein to encapsidate pre-genomic RNA and form immature capsid particles in the cytoplasm. This step is prerequisite for viral DNA replication. The HBV capsid spontaneously self-assembles from many copies of core dimers present in the cytoplasm. It has been shown that the formation of a trimeric nucleus and the subsequent elongation reactions occur by adding one dimeric subunit at a time until it is complete. Besides this function, capsid protein regulates viral DNA synthesis through different phosphorylation status of its C-terminal phosphorylation sites. When a near full-length relaxed circular DNA is formed through reverse-transcription of viral pregenomic RNA, an immature capsid becomes a mature capsid. On one hand, capsid protein might facilitate the nuclear translocation of viral relaxed circular genome by means of the nuclear localization signals located in the Arginine-rich domain of the C-terminal region of capsid protein. In nucleus, as a component of viral cccDNA minichromosome, capsid protein could play a structural and regulatory role in the functionality of cccDNA minichromosomes. Capsid protein also interacts with viral large envelope protein in endoplasmic reticulum and triggers the release of intact viral particles from hepatocytes.

There has been a couple of capsid related anti-HBV inhibitors reported. For example, phenylpropenamide derivatives, including compounds named AT-61 and AT-130 (Feld J. et al. Antiviral Research **2007**, 168-177), and a class of thiazolidin-4-ones from Valeant R&D (WO2006/033995), have been shown to inhibit pgRNA packaging. A recent study suggested that phenylpropenamides are, in fact, accelerators of HBV capsid assembly, and their actions result in

the formation of empty capsids. These very interesting results illustrate the importance of the kinetic pathway in successful virus assembly.

Heteroaryldihydropyrimidines or HAP, including compounds named Bay 41-4109, Bay 38-7690 and Bay 39-5493, were discovered in a tissue culture-based screening (Deres K. et al. Science **2003**, 893). These HAP analogs act as synthetic allosteric activators and are able to induce aberrant capsid formation that leads to degradation of the core protein. HAP analogs also reorganized core protein from preassembled capsids into noncapsid polymers, presumably by interaction of HAP with dimers freed during capsid ‘breathing’, the transitory breaking of individual intersubunit bonds. Bay 41-4109 was administered to HBV infected transgenic mouse or humanized mouse models and demonstrated in vivo efficacy with HBV DNA reduction (Deres K. et al. Science **2003**, 893; Brezillon N. et al. PLoS ONE **2011**, e25096). It was also shown that bis-ANS, a small molecule that acts as a molecular ‘wedge’ and interferes with normal capsid-protein geometry and capsid formation (Zlotnick A. et al. J. Virol. **2002**, 4848-4854).

SUMMARY OF THE INVENTION

Objects of the present invention are novel compounds of formula I, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I for the treatment or prophylaxis of HBV infection.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used herein, the term “C₁₋₆alkyl” alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, propyl, isopropyl, 1-butyl, 2-butyl, tert-butyl and the like. Particular “C₁₋₆alkyl” groups are methyl, ethyl, isopropyl and tert-butyl.

The term “cycloalkyl”, alone or in combination, refers to a saturated carbon ring containing from 3 to 7 carbon atoms, particularly from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Particular “cycloalkyl” groups are cyclopropyl, cyclopentyl and cyclohexyl.

The term “-C_xH_{2x}-” alone or in combination signifies a saturated, linear or branched chain alkyl group containing from 1 to 6 carbon atoms, particularly from 1 to 4 carbon atoms.

The term “-C_yH_{2y}-” alone or in combination signifies a chemical link or a saturated, linear or branched chain alkyl group containing from 1 to 6 carbon atoms, particularly, the term signifies a chemical link or a saturated, linear or branched chain alkyl group containing from 1 to 4 carbon atoms.

- 5 The term “C₁₋₆alkoxy” alone or in combination signifies a group C₁₋₆alkyl-O-, wherein the “C₁₋₆alkyl” is as defined above; for example methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, i-butoxy, 2-butoxy, t-butoxy and the like. Particular C₁₋₆alkoxy groups are methoxy and ethoxy and more particularly methoxy.

The term “amino”, alone or in combination, refers to primary (-NH₂), secondary (-NH-) or

- 10 tertiary amino ().

The term “carboxy” alone or in combination refers to the group -COOH.

The term “cyano” alone or in combination refers to the group -CN.

The term “halogen” means fluorine, chlorine, bromine or iodine. Halogen is particularly fluorine, chlorine or bromine.

- 15 The term “hydroxy” alone or in combination refers to the group -OH.

The term “sulfonyl” alone or in combination refers to the group -S(O)₂-.

The term “carbonyl” alone or in combination refers to the group -C(O)-.

The term “carboxy-C_yH_{2y}-” refers to a group “-C_yH_{2y}-COOH”, wherein the “-C_yH_{2y}-” is as defined above.

- 20 The term “hydroxy-C_yH_{2y}-” refers to a group “-C_yH_{2y}-OH”, wherein the “-C_yH_{2y}-” is as defined above.

The term “C₁₋₆alkoxycarbonyl” refers to a group C₁₋₆alkoxy-C(O)-, wherein the “C₁₋₆alkoxy” is as defined above.

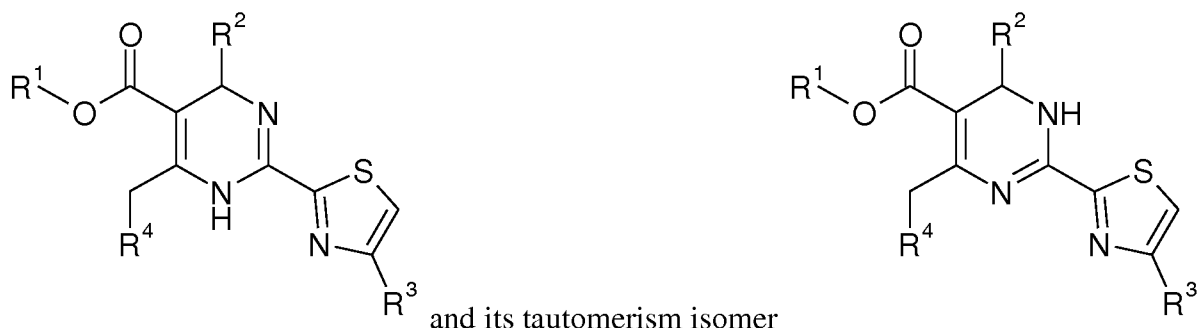
- 25 The term “C₁₋₆alkylcarbonyl” refers to a group C₁₋₆alkyl-C(O)-, wherein the “C₁₋₆alkyl” is as defined above.

The term “aminocarbonyl” refers to a group amino-C(O)-, wherein the “amino” is as defined above.

The term “C₁₋₆alkylsulfonyl” refers to a group C₁₋₆alkyl-S(O)₂-, wherein the “C₁₋₆alkyl” is as defined above.

- 30 The term “aminosulfonyl” refers to a group amino-S(O)₂-, wherein the “amino” is as defined above.

The term “tautomerism isomers” refers to constitutional isomers of organic compounds that readily interconvert by a chemical reaction called tautomerization. This reaction commonly results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond. For example, compounds of general formula (I)



The term “enantiomer” denotes two stereoisomers of a compound which are non-superimposable mirror images of one another.

The term “diastereomer” denotes a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another.

10 The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term “pharmaceutically acceptable salt” refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those
 15 derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those
 20 derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin R.J., et al., Organic Process Research & Development 2000, 4, 427-435; or in Ansel, H., et al., In: Pharmaceutical Dosage Forms and
 25 Drug Delivery Systems, 6th ed. (1995), pp. 196 and 1456-1457. Particular are the sodium salts of the compounds of formula I.

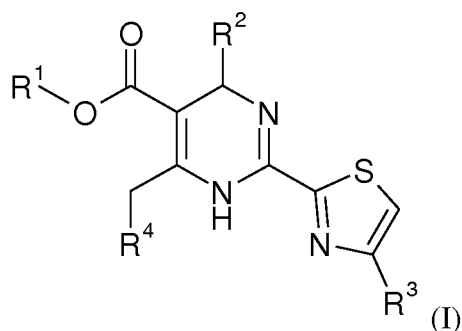
Compounds of the general formula I which contain one or several chiral centers can either be present as racemates, diastereomeric mixtures, or optically active single isomers. The

racemates can be separated according to known methods into the enantiomers. Particularly, diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid.

5

INHIBITORS OF HBV

The present invention provides (i) novel compounds having the general formula I:



wherein

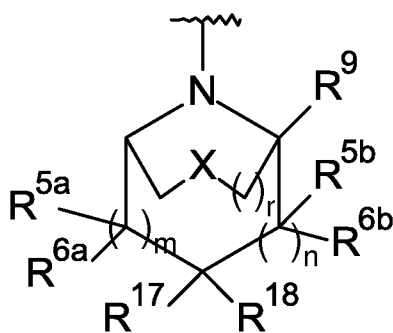
10

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

R^2 is phenyl, which is once or twice or three times substituted by halogen or C_{1-6} alkyl;

R^3 is hydrogen or C_{1-6} alkyl;

R^4 is



15

wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen, halogen or hydroxy;

one of R^{5b} and R^{6b} is hydrogen or halogen, and the other one is hydrogen or halogen;

R^9 is hydrogen or carboxy;

20

one of R^{17} and R^{18} is hydrogen, halogen, hydroxy, amino, C_{1-6} alkylsulfonylamino or trifluoromethylcarbonylamino, the other one is hydrogen, halogen, hydroxy- $C_yH_{2y}-$, C_{1-6} alkylcarbonyl-O-, C_{1-6} alkoxycarbonyl-

-7-

C_yH_{2y} -, carboxy- C_yH_{2y} -O-, carboxy- C_yH_{2y} -, C_{1-6} alkylcarbonyl-NH-, C_{1-6} alkylsulfonyl-NH-, aminocarbonyl-NH- or aminosulfonyl-NH-;

wherein $-C_yH_{2y}$ - is unsubstituted once or more times substituted by hydroxy;

or R^{6a} and R^{17} together with the carbon atoms, to which they are attached, form a ring of isoxazolyl, pyrazolyl or oxo-dihydropyrazolyl, which ring is unsubstituted or once or more times substituted by C_{1-6} alkyl;

or R^{17} and R^{18} together with the carbon atom, to which they are attached, form diazirinyl;

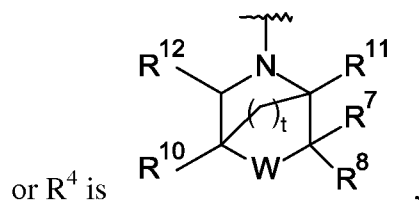
X is oxygen; sulfur; -N(carbonyl C_{1-6} alkyl)-; or -C($R^{15}R^{16}$)-, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen or carboxy- C_yH_{2y} ;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

y is 0-6;



wherein R^7 is hydrogen or halogen;

R^8 is hydrogen or halogen;

R^{10} is hydrogen, halogen, hydroxy- C_yH_{2y} - or C_{1-6} alkylcarbonylamino- C_yH_{2y} ;

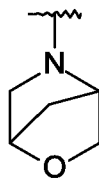
R^{11} is hydrogen or carboxy;

R^{12} is hydrogen or carboxy;

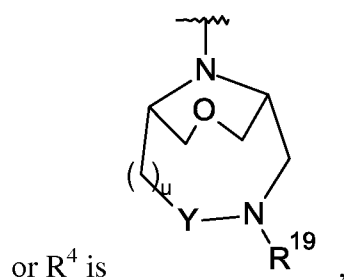
W is a bond, oxygen, $-CH_2-$, $-CF_2-$ or -N(carbonyl C_{1-6} alkyl)-;

t is 1 or 2;

y is 0-6;



with the proviso that is excluded;

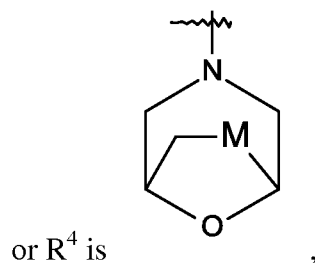


wherein R¹⁹ is hydrogen; C₁₋₆alkyl, which is unsubstituted or once or more times substituted by halogen; C₁₋₆alkoxycarbonyl-C_yH_{2y}-; hydroxy-C_yH_{2y}-carbonyl; carboxy-C_yH_{2y}-carbonyl; C₁₋₆alkylaminosulfonyl; C₁₋₆alkylcarbonyl; C₁₋₆alkylsulfonyl; aminocarbonyl; or aminosulfonyl;

Y is carbonyl or -CH₂-;

u is 0 or 1;

y is 0-6;



wherein M is a bond, -CH₂- or -N(R¹⁴)-CH₂-;

R¹⁴ is C₁₋₆alkoxycarbonyl;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

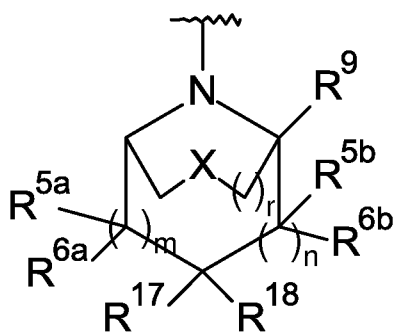
Another embodiment of present invention is (ii) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

R¹ is methyl or ethyl;

R² is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

R³ is hydrogen or methyl;

R⁴ is



wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen, fluoro or hydroxy;

one of R^{5b} and R^{6b} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, fluoro, hydroxy, amino, methylsulfonylamino or trifluoromethylcarbonylamino, the other one is hydrogen, fluoro, hydroxy, hydroxymethyl, methylcarbonyl-O-, methoxycarbonyl,

methoxycarbonylmethyl, ethoxycarbonylmethyl,

methoxycarbonyl(hydroxy)methyl, ethoxycarbonyl(hydroxy)methyl,

carboxymethyl-O-, carboxy, carboxymethyl, methylcarbonylamino, aminocarbonylamino, methylsulfonylamino or aminosulfonylamino;

or R^{6a} and R^{17} together with the carbon atoms, to which they are attached, form a ring of isoxazolyl, pyrazolyl or oxo-dihydropyrazolyl, which ring is unsubstituted or once or more times substituted by methyl;

or R^{17} and R^{18} together with the carbon atom, to which they are attached, form diazirinyl;

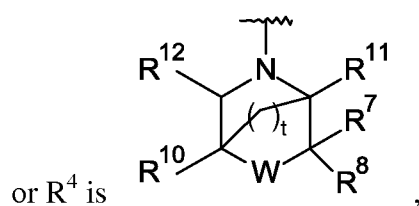
X is oxygen; sulfur; -N(carbonylmethyl)-; or -C($R^{15}R^{16}$)-, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen, carboxy or carboxymethyl;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

-10-



wherein R⁷ is hydrogen or fluoro;

R⁸ is hydrogen or fluoro;

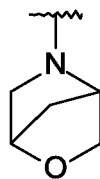
R¹⁰ is hydrogen, fluoro, hydroxymethyl or methylcarbonylaminomethyl;

R¹¹ is hydrogen or carboxy;

R¹² is hydrogen or carboxy;

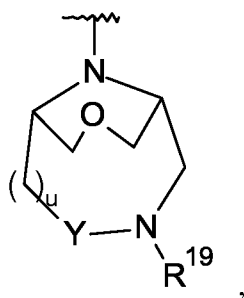
W is a bond, oxygen, -CH₂-, -CF₂- or -N(carbonylmethyl)-;

t is 1 or 2;



with the proviso that

is excluded;



or R⁴ is

wherein R¹⁹ is hydrogen, methyl, isopropyl, difluoromethylmethyl,

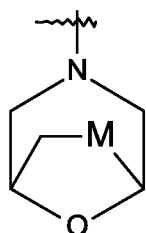
methylcarbonyl, methoxycarbonyl, ethoxycarbonylisopropyl,

hydroxymethylcarbonyl, carboxyisopropylcarbonyl, aminocarbonyl,

methylsulfonyl, aminosulfonyl or methylaminosulfonyl;

Y is carbonyl or -CH₂-;

u is 0 or 1;



or R⁴ is

-11-

wherein M is a bond, -CH₂- or -N(carbonyltert-butoxy)-CH₂-;
or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

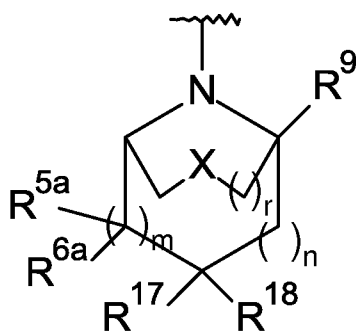
Another embodiment of present invention is (iii) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

R¹ is C₁₋₆alkyl;

R² is phenyl, which is once or twice or three times substituted by halogen or C₁₋₆alkyl;

R³ is hydrogen or C₁₋₆alkyl;

R⁴ is



wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen or halogen;

R⁹ is hydrogen or carboxy;

one of R¹⁷ and R¹⁸ is hydrogen or C₁₋₆alkylsulfonylamino, the other one is hydrogen, C₁₋₆alkoxycarbonyl-C_yH_{2y}-, carboxy-C_yH_{2y}-O-, carboxy-C_yH_{2y}-, C₁₋₆alkylcarbonyl-NH-, C₁₋₆alkylsulfonyl-NH- or aminosulfonyl-NH-;

or R^{6a} and R¹⁷ together with the carbon atoms, to which they are attached, form pyrazolyl;

X is oxygen; sulfur; or -C(R¹⁵R¹⁶)-, wherein one of R¹⁵ and R¹⁶ is hydrogen or hydroxy, and the other one is hydrogen or carboxy-C_yH_{2y}-;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

y is 0-6.

-12-

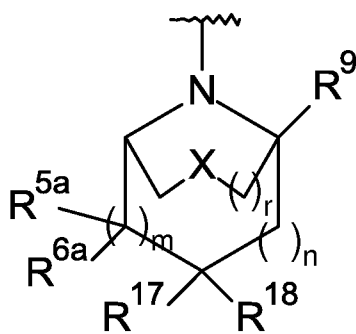
Further embodiment of present invention is (iv) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

R^1 is methyl or ethyl;

5 R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

R^3 is hydrogen or methyl;

R^4 is



10 wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen or methylsulfonylamino, the other one is hydrogen, ethoxycarbonylmethyl, carboxymethyl-O-, carboxy, carboxymethyl, methylcarbonyl-NH-, methylsulfonyl-NH- or aminosulfonyl-NH-;

15 or R^{6a} and R^{17} together with the carbon atoms, to which they are attached, form pyrazolyl;

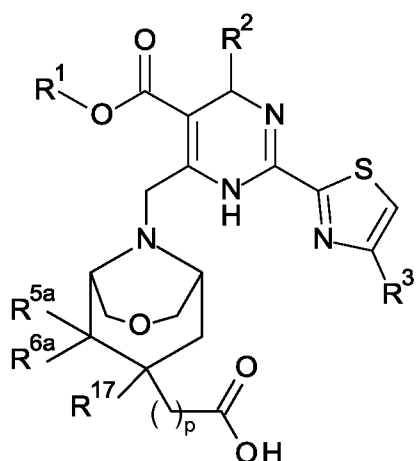
X is oxygen; sulfur; or $-C(R^{15}R^{16})-$, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen, carboxy or carboxymethyl;

20 r is 0 or 1;

m is 0 or 1;

n is 0 or 1.

Another embodiment of present invention is (v) a compound of formula IA



(IA)

wherein

R¹ is C₁₋₆alkyl;

R² is phenyl, which is once or twice or three times substituted by halogen or C₁₋₆alkyl;

5 R³ is hydrogen or C₁₋₆alkyl;

one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen, halogen or hydroxy;

R¹⁷ is hydrogen or amino;

p is 0 or 1;

10 or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

Further embodiment of present invention is (vi) a compound of formula IA or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers

15 thereof, wherein

R¹ is methyl or ethyl;

R² is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

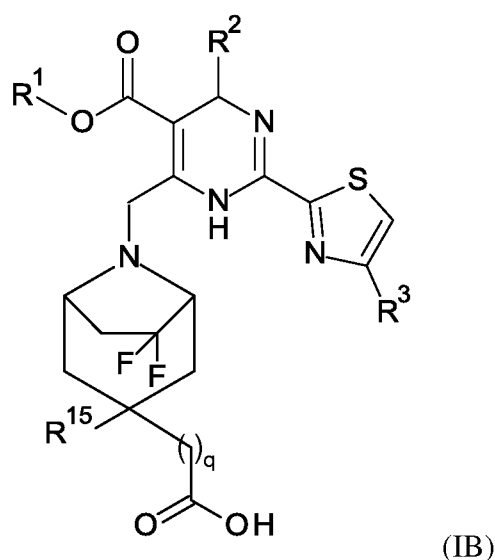
R³ is hydrogen or methyl;

20 one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen, fluoro or hydroxy;

R¹⁷ is hydrogen or amino;

p is 0 or 1.

Another embodiment of present invention is (vii) a compound of formula IB



wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen or C_{1-6} alkyl;

5 R^3 is hydrogen;

R^{15} is hydrogen or hydroxy;

q is 0 or 1;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

10

Another embodiment of present invention is (viii) a compound of formula IB or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

R^1 is methyl or ethyl;

15 R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

R^3 is hydrogen;

R^{15} is hydrogen or hydroxy;

q is 0 or 1.

20

Another embodiment of present invention is (ix) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

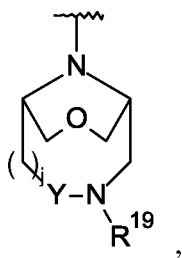
R^1 is C_{1-6} alkyl;

-15-

R^2 is phenyl, which is once or twice or three times substituted by halogen;

R^3 is hydrogen;

R^4 is



5 wherein R^{19} is hydrogen, aminocarbonyl, aminosulfonyl or hydroxy- C_yH_{2y} -carbonyl;

Y is $-CH_2-$ or carbonyl;

j is 0 or 1;

y is 0-6.

10

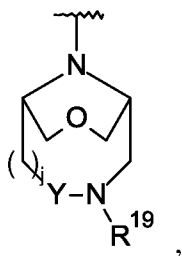
Further embodiment of present invention is (x) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

R^1 is methyl;

15 R^2 is phenyl, which is once or twice or three times substituted by fluoro or chloro;

R^3 is hydrogen;

R^4 is



wherein R^{19} is hydrogen, aminocarbonyl, aminosulfonyl or

20 hydroxymethylcarbonyl;

Y is $-CH_2-$ or carbonyl;

j is 0 or 1.

-16-

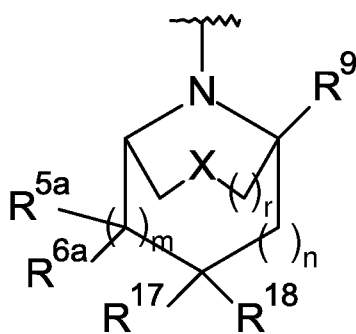
Another embodiment of present invention is (xi) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

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

5 R^2 is phenyl, which is once or twice or three times substituted by halogen;

R^3 is hydrogen;

R^4 is



wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen or halogen;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, the other one is hydrogen or carboxy- C_yH_{2y} -;

X is oxygen; or $-C(R^{15}R^{16})-$, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen or carboxy- C_yH_{2y} -;

15 r is 0 or 1;

m is 1;

n is 0 or 1;

y is 0-6.

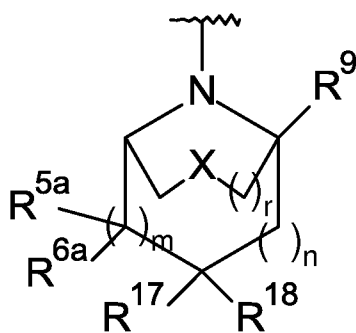
20 Another embodiment of present invention is (xii) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

R^1 is methyl or ethyl;

R^2 is phenyl, which is once or twice or three times substituted by fluoro or chloro;

25 R^3 is hydrogen;

R^4 is



wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

R⁹ is hydrogen or carboxy;

5 one of R¹⁷ and R¹⁸ is hydrogen, the other one is hydrogen or carboxymethyl;

X is oxygen; or -C(R¹⁵R¹⁶)-, wherein one of R¹⁵ and R¹⁶ is hydrogen or hydroxy, and the other one is hydrogen or carboxymethyl;

r is 0 or 1;

m is 1;

10 n is 0 or 1.

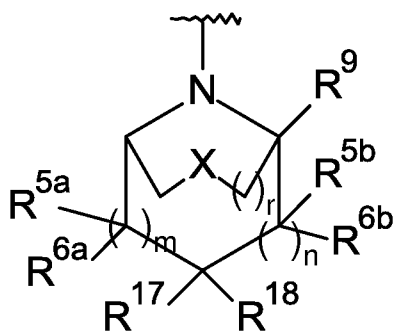
Another embodiment of present invention is (xiii) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

15 R¹ is C₁₋₆alkyl;

R² is phenyl, which is once or twice or three times substituted by halogen or C₁₋₆alkyl;

R³ is hydrogen or C₁₋₆alkyl;

R⁴ is



20 wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen, halogen or hydroxy;

-18-

one of R^{5b} and R^{6b} is hydrogen, and the other one is hydrogen or carboxy- C_yH_{2y} -;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen or amino, the other one is hydrogen, carboxy- C_yH_{2y} -O-, carboxy- C_yH_{2y} -, C_{1-6} alkylcarbonyl-NH-, C_{1-6} alkylsulfonyl-NH-, aminocarbonyl-NH- or aminosulfonyl-NH-;

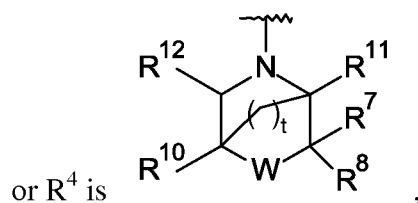
X is oxygen; -N(carbonyl C_{1-6} alkyl)- or -C($R^{15}R^{16}$)-, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen or carboxy- C_yH_{2y} ;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

y is 0-6;



wherein R^7 is hydrogen;

R^8 is hydrogen;

R^{10} is hydrogen, halogen or hydroxy- C_yH_{2y} -;

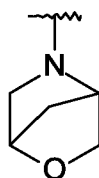
R^{11} is hydrogen or carboxy;

R^{12} is hydrogen or carboxy;

W is a bond, oxygen or -CH₂-;

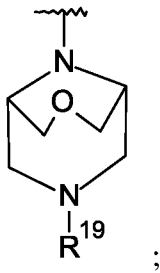
t is 1 or 2;

y is 0-6;



with the proviso that is excluded;

or R^4 is



wherein R¹⁹ is hydroxy-C_yH_{2y}-carbonyl, carboxy-C_yH_{2y}-carbonyl, C₁₋₆alkylsulfonyl, aminocarbonyl or aminosulfonyl;
y is 0-6.

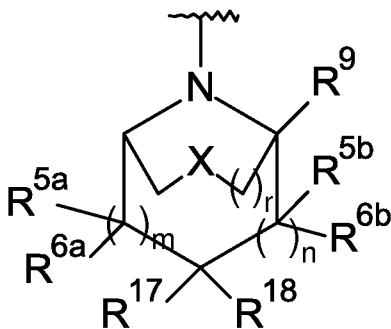
5

Further embodiment of present invention is (xiv) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

R¹ is methyl or ethyl;

10 R² is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

R³ is hydrogen or methyl;

 $\mathbb{R}^4$ is

15 wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen, fluoro or hydroxy;

one of R^{5b} and R^{6b} is hydrogen, and the other one is hydrogen or carboxymethyl;

R⁹ is hydrogen or carboxy;

one of R¹⁷ and R¹⁸ is hydrogen or amino, the other one is hydrogen, carboxy, carboxymethyl, carboxymethyl-O-, methylcarbonylamino, aminocarbonylamino, methylsulfonylamino or aminosulfonylamino;

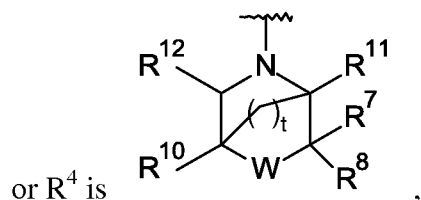
-20-

X is oxygen; -N(carboxymethyl)-; or -C(R¹⁵R¹⁶)-, wherein one of R¹⁵ and R¹⁶ is hydrogen or hydroxy, and the other one is hydrogen, carboxy, or carboxymethyl;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;



wherein R⁷ is hydrogen;

R⁸ is hydrogen;

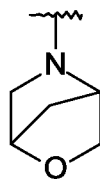
R¹⁰ is hydrogen, fluoro or hydroxymethyl;

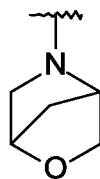
R¹¹ is hydrogen or carboxy;

R¹² is hydrogen or carboxy;

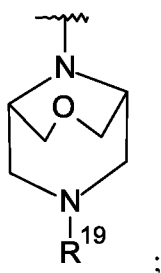
W is a bond, oxygen or -CF₂-;

t is 1 or 2.



with the proviso that  is excluded;

or R⁴ is



wherein R¹⁹ is hydroxymethylcarbonyl, carboxyisopropylcarbonyl, aminocarbonyl, methylsulfonyl or aminosulfonyl.

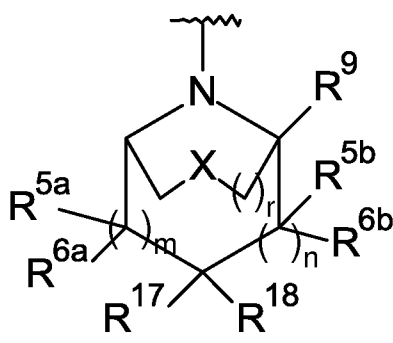
Another embodiment of present invention is (xv) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

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

5 R^2 is phenyl, which is once or twice or three times substituted by halogen or C_{1-6} alkyl;

R^3 is hydrogen or C_{1-6} alkyl;

R^4 is



wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen, halogen or hydroxy;

one of R^{5b} and R^{6b} is hydrogen or halogen, and the other one is hydrogen or halogen;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, hydroxy or amino, the other one is hydroxy- C_yH_{2y} -, carboxy- C_yH_{2y} -O-, carboxy- C_yH_{2y} -, or C_{1-6} alkylcarbonyl-NH-;

or R^{6a} and R^{17} together with the carbon atoms, to which they are attached, form a ring of oxo-dihydropyrazolyl, which ring is unsubstituted or once or more times substituted by C_{1-6} alkyl;

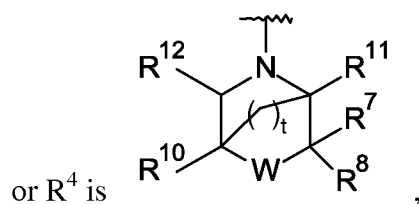
X is oxygen; sulfur; or $-C(R^{15}R^{16})-$, wherein one of R^{15} and R^{16} is hydrogen, and the other one is hydrogen or carboxy- C_yH_{2y} -;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

y is 0-6;



wherein R⁷ is hydrogen;

R⁸ is hydrogen;

R¹⁰ is hydrogen, halogen, hydroxy-C_yH_{2y}- or C₁₋₆alkylcarbonylamino-C_yH_{2y}-;

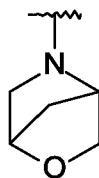
R¹¹ is hydrogen or carboxy;

R¹² is hydrogen or carboxy;

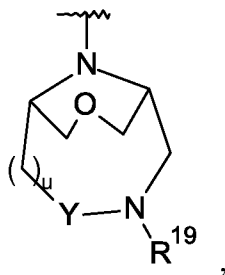
W is a bond, oxygen, -CF₂-, or -N(carbonylC₁₋₆alkyl)-;

t is 1 or 2;

y is 0-6;



with the proviso that 0 is excluded;



wherein R¹⁹ is hydrogen, C₁₋₆alkyl, hydroxy-C_yH_{2y}-carbonyl, carboxy-C_yH_{2y}-carbonyl, C₁₋₆alkylcarbonyl or aminocarbonyl;

Y is carbonyl or -CH₂-;

u is 0 or 1;

y is 0-6.

Further embodiment of present invention is (xvi) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

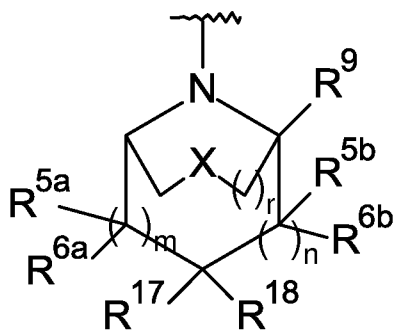
R¹ is methyl or ethyl;

-23-

R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

R^3 is hydrogen or methyl;

R^4 is



wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen, fluoro or hydroxy;

one of R^{5b} and R^{6b} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, hydroxy or amino, the other one is hydroxy, carboxymethyl-O-, carboxy, carboxymethyl or methylcarbonylamino;

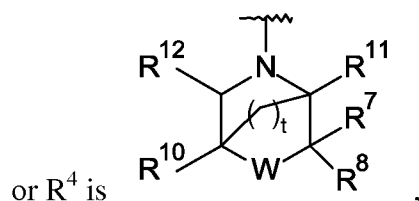
or R^{6a} and R^{17} together with the carbon atoms, to which they are attached, form a ring of oxo-dihydropyrazolyl, which ring is unsubstituted or once or more times substituted by methyl;

X is oxygen; sulfur; or $-C(R^{15}R^{16})-$, wherein one of R^{15} and R^{16} is hydrogen, and the other one is hydrogen carboxymethyl;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;



wherein R^7 is hydrogen;

R^8 is hydrogen;

R^{10} is hydrogen, fluoro, hydroxymethyl or methylcarbonylaminomethyl;

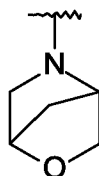
-24-

R^{11} is hydrogen or carboxy;

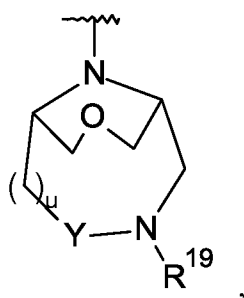
R^{12} is hydrogen or carboxy;

W is a bond, oxygen, $-\text{CF}_2-$, or $-\text{N}(\text{carbonylmethyl})-$;

t is 1 or 2;



5 with the proviso that is excluded;



or R^4 is

wherein R^{19} is hydrogen, methyl, isopropyl, methylcarbonyl, hydroxymethylcarbonyl, carboxyisopropylcarbonyl or aminocarbonyl;

Y is carbonyl or $-\text{CH}_2-$;

10 u is 0 or 1.

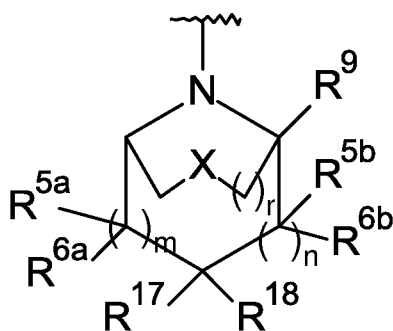
Another embodiment of present invention is (xvii) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen or C_{1-6} alkyl;

R^3 is hydrogen or C_{1-6} alkyl;

R^4 is



wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen or halogen;

one of R^{5b} and R^{6b} is hydrogen or halogen, and the other one is hydrogen or halogen;

R⁹ is hydrogen or carboxy; one of R¹⁷ and R¹⁸ is hydrogen, halogen, hydroxy, C₁₋₆alkylsulfonylamino or trifluoromethylcarbonylamino, the other one is hydrogen, halogen, hydroxy-C_yH_{2y}-, C₁₋₆alkoxycarbonyl-C_yH_{2y}-, carboxy-C_yH_{2y}-, C₁₋₆alkylcarbonyl-NH-, C₁₋₆alkylsulfonyl-NH-, aminocarbonyl-NH- or aminosulfonyl-NH-;

wherein -C_yH_{2y}- is unsubstituted once or more times substituted by hydroxy;

or R^{6a} and R¹⁷ together with the carbon atoms, to which they are attached, form a ring of isoxazolyl, pyrazolyl or oxo-dihydropyrazolyl, which ring is unsubstituted or once or more times substituted by C₁₋₆alkyl;

or R¹⁷ and R¹⁸ together with the carbon atom, to which they are attached, form diazirinyl;

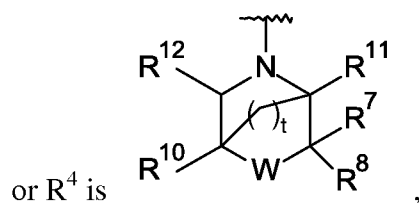
X is oxygen; or -C(R¹⁵R¹⁶)-, wherein one of R¹⁵ and R¹⁶ is hydrogen or hydroxy, and the other one is carboxy-C_vH_{2v}-;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

y is 0-6;



wherein R⁷ is hydrogen;

R⁸ is hydrogen;

R¹⁰ is hydroxy-C_vH_{2v}-;

R¹¹ is hydrogen;

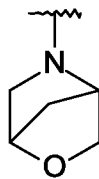
R¹² is hydrogen;

W is oxygen;

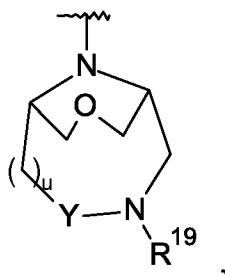
t is 1;

-26-

y is 0-6;



with the proviso that is excluded;

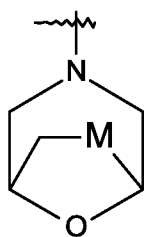
or R⁴ is

wherein R¹⁹ is C₁₋₆alkyl, which is unsubstituted or once or more times substituted by halogen; C₁₋₆alkoxycarbonyl-C_yH_{2y}-; C₁₋₆alkylsulfonyl; aminocarbonyl; or aminosulfonyl;

Y is -CH₂-;

u is 0;

y is 0-6;

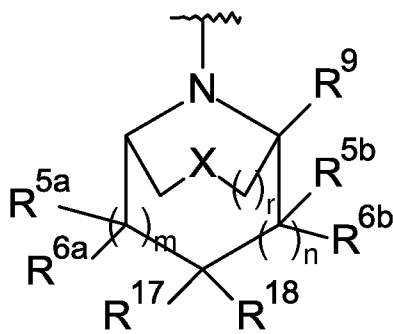
or R⁴ iswherein M is a bond or -CH₂-.

Further embodiment of present invention is (xviii) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

R¹ is methyl or ethyl;

R² is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

R³ is hydrogen or methyl;R⁴ is



wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

one of R^{5b} and R^{6b} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

R⁹ is hydrogen or carboxy;

one of R¹⁷ and R¹⁸ is hydrogen, fluoro, hydroxy, methylsulfonylamino or trifluoromethylcarbonylamino, the other one is hydrogen, fluoro, hydroxy, hydroxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl,

ethoxycarbonyl(hydroxy)methyl, carboxy, carboxymethyl, methylcarbonylamino, aminocarbonylamino, methylsulfonylamino or aminosulfonylamino;

or R^{6a} and R¹⁷ together with the carbon atoms, to which they are attached, form a ring of isoxazolyl, pyrazolyl or oxo-dihydropyrazolyl, which ring is unsubstituted or once or more times substituted by methyl;

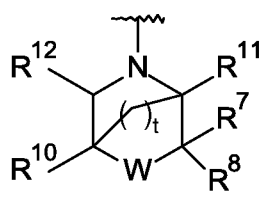
or R¹⁷ and R¹⁸ together with the carbon atom, to which they are attached, form diazirinyl;

X is oxygen; or -C(R¹⁵R¹⁶)-, wherein one of R¹⁵ and R¹⁶ is hydrogen or hydroxy, and the other one is carboxy or carboxymethyl;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

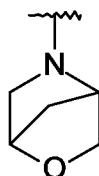


wherein R⁷ is hydrogen;

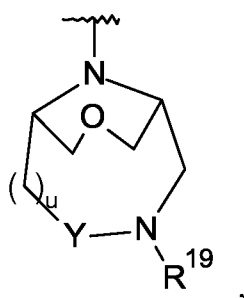
-28-

R^8 is hydrogen;
 R^{10} is hydrogen, or hydroxymethyl;
 R^{11} is hydrogen;
 R^{12} is hydrogen;
 W is oxygen;
 t is 1;

5



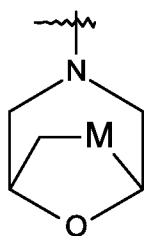
with the proviso that is excluded;



or R^4 is

wherein R^{19} is difluoromethylmethyl, methoxycarbonyl, aminocarbonyl,
 methylsulfonyl or aminosulfonyl;
 Y is $-CH_2-$;
 u is 0;

10



or R^4 is

wherein M is a bond or $-CH_2-$.

15

Another embodiment of present invention is (xix) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

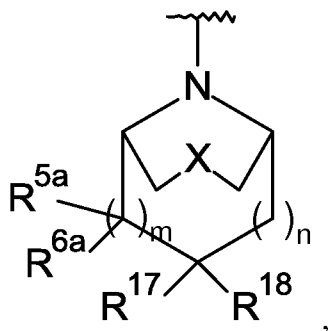
R^1 is C_{1-6} alkyl;

20

R^2 is phenyl, which is once or twice or three times substituted by halogen;

R^3 is hydrogen;

R⁴ is



wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen or halogen;

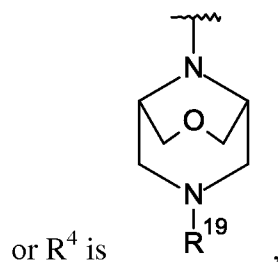
5 one of R¹⁷ and R¹⁸ is hydrogen, the other one is hydrogen, carboxy-C_yH_{2y}-, C₁-₆alkylcarbonyl-NH- or aminosulfonyl-NH-;
or R^{6a} and R¹⁷ together with the carbon atoms, to which they are attached, form pyrazolyl;

X is oxygen or -C(carboxyC₁₋₆alkyl)-;

10 m is 0 or 1;

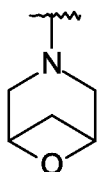
n is 0 or 1;

y is 0-6;



wherein R¹⁹ is C₁₋₆alkyl;

15 or R⁴ is



Further embodiment of present invention is (xx) a compound of formula I or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

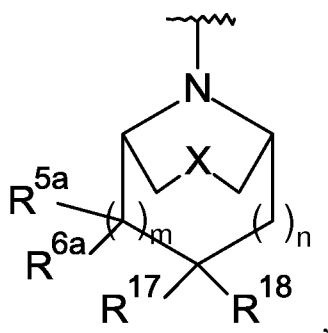
20 R¹ is methyl or ethyl;

-30-

R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro or bromo;

R^3 is hydrogen;

R^4 is



5 wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

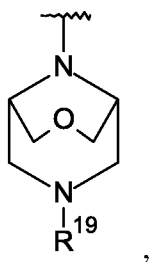
one of R^{17} and R^{18} is hydrogen, the other one is hydrogen, carboxymethyl, methylcarbonylamino or aminosulfonylamino;

10 or R^{6a} and R^{17} together with the carbon atoms, to which they are attached, form pyrazolyl;

X is oxygen or -C(carboxymethyl)-;

m is 0 or 1;

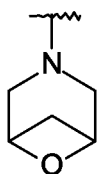
n is 0 or 1;



15 or R^4 is

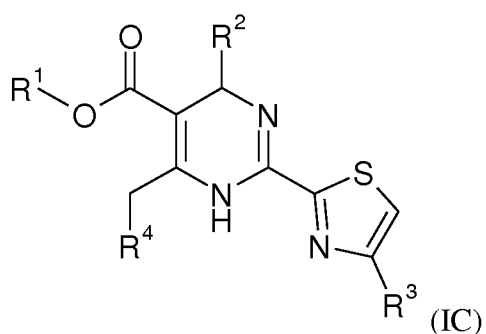
wherein R^{19} is methyl;

or R^4 is



20 Another embodiment of present invention is (xxi) a compound of formula IC, wherein

-31-

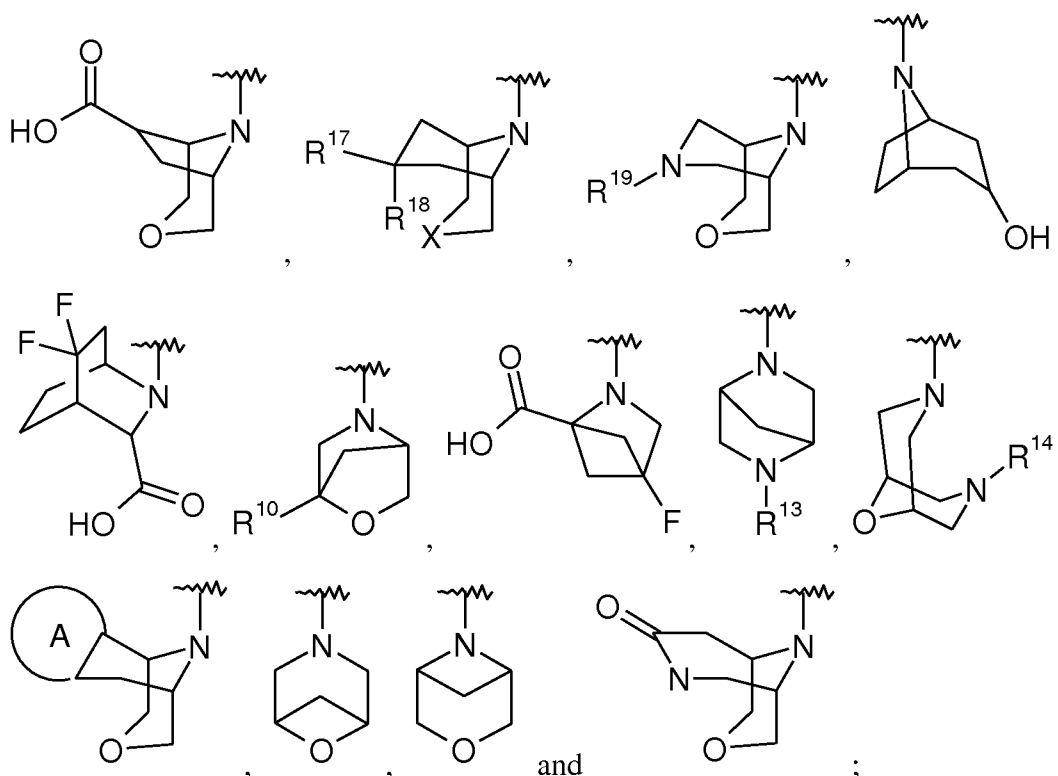


R^1 is C_{1-6} alkyl;

R^2 is phenyl, which is once or twice or three times substituted by halogen;

5 R^3 is hydrogen or C_{1-6} alkyl;

R^4 is selected from



10 wherein R^{10} is hydroxy- C_yH_{2y-} ;

R^{13} is C_{1-6} alkylcarbonyl;

R^{14} is C_{1-6} alkoxycarbonyl;

X is -O- or -S-; provided that

when X is -O-, R^{17} is hydrogen or hydroxy, R^{18} is C_{1-6} alkoxycarbonyl- C_yH_{2y-} , carboxy-

15 C_yH_{2y-} , hydroxy- C_yH_{2y-} , C_{1-6} alkylcarbonyl-O-, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino

-32-

$$\text{C}_{1-6}\text{alkoxycarbonyl}-\text{C}_x\text{H}_{2x}-\text{OH}$$
 or $\text{C}_x\text{H}_{2x}-\text{N}=\text{N}-$, or R^{17} and R^{18} , together with the carbon atom, to which

they are attached, form $\text{N}=\text{N}-$;

when X is -S-, R^{17} is hydrogen, R^{18} is carboxy- C_yH_{2y} -;

R^{19} is selected from aminocarbonyl; aminosulfonyl; $\text{C}_{1-6}\text{alkoxycarbonyl}-\text{C}_y\text{H}_{2y}$ -; $\text{C}_{1-6}\text{alkyl}$,
 5 which is unsubstituted or substituted by fluoro; $\text{C}_{1-6}\text{alkylaminosulfonyl}$; $\text{C}_{1-6}\text{alkylcarbonyl}$; $\text{C}_{1-6}\text{alkylsulfonyl}$ and hydroxy- C_xH_{2x} -carbonyl;

A is pyrazolyl or oxypyrazolyl, which is unsubstituted or substituted by $\text{C}_{1-6}\text{alkyl}$;

x is 1-6;

y is 0-6;

10 or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

Further embodiment of present invention is (xxii) a compound of formula IC, wherein

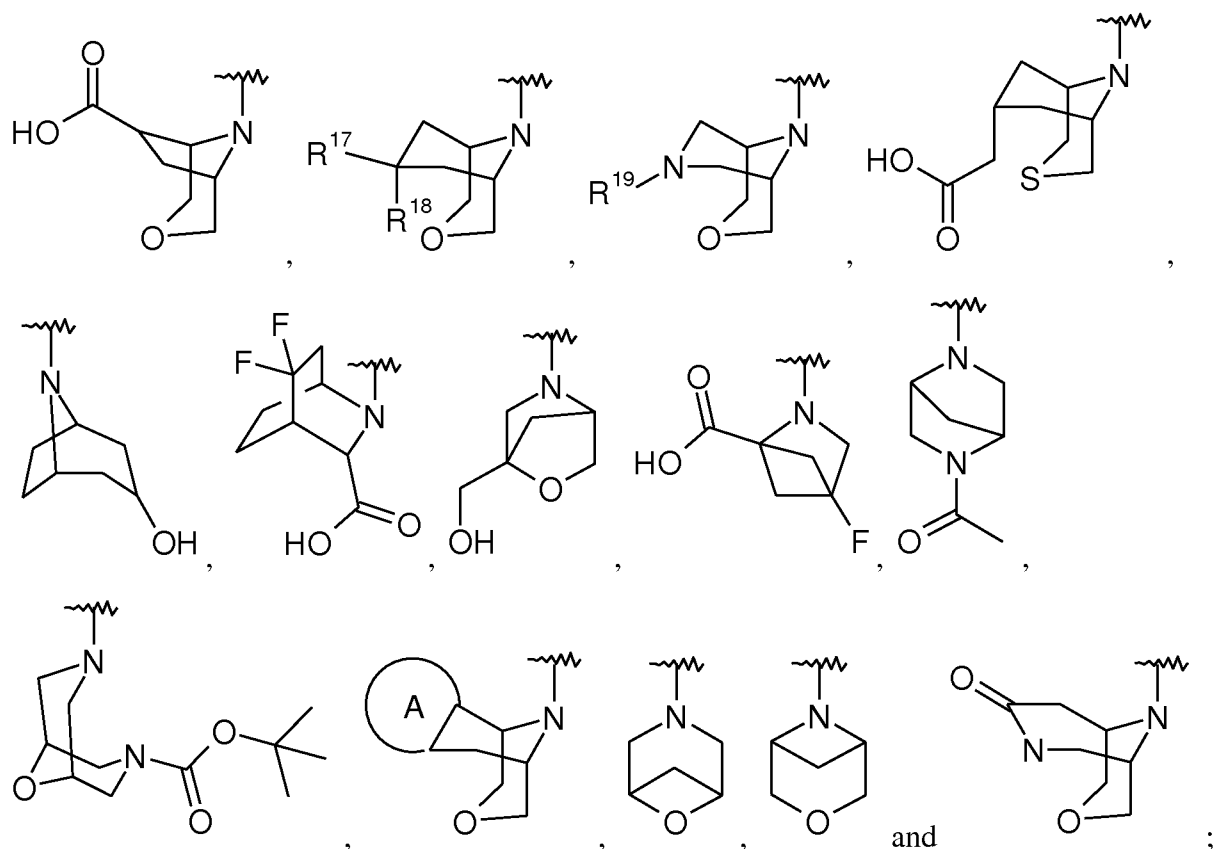
R^1 is methyl or ethyl;

15 R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro or bromo;

R^3 is hydrogen or methyl;

R^4 is selected from

-33-



wherein R¹⁷ is hydrogen or hydroxy;

- 5 R¹⁸ is methoxycarbonyl, methoxycarbonylmethyl, methoxycarbonylmethyl(hydroxy), carboxy, carboxymethyl, hydroxy, hydroxymethyl, methylcarbonyl-O-, methylcarbonylamino or methylsulfonylamino;

or R¹⁷ and R¹⁸, together with the carbon atom, to which they are attached, form  ;

- 10 R¹⁹ is aminocarbonyl, aminosulfonyl, methoxycarbonyl, ethoxycarbonylisopropyl, methyl, isopropyl, difluoroethyl, methylaminosulfonyl, methylcarbonyl, methylsulfonyl or hydroxymethylcarbonyl;

A is pyrazolyl or oxypyrazolyl, which is unsubstituted or substituted by methyl; or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

15

Another embodiment of present invention is (xxiii) a compound of formula IC, wherein

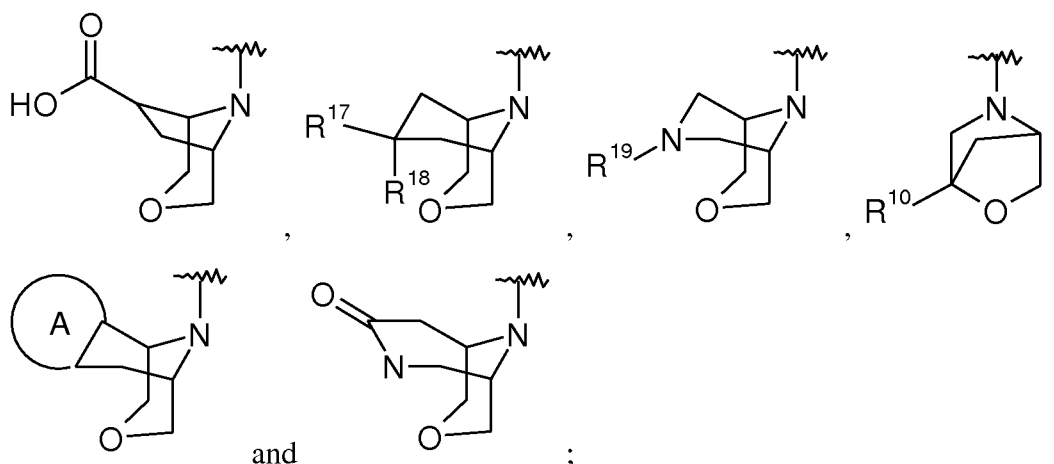
R¹ is C₁₋₆alkyl;

R² is phenyl, which is once or twice or three times substituted by halogen;

R³ is hydrogen;

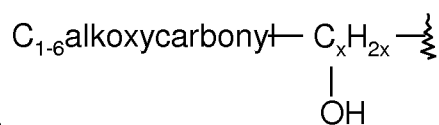
-34-

R^4 is selected from



wherein R^{10} is hydroxy- C_xH_{2x} -;

5 R^{17} is hydrogen, R^{18} is C_{1-6} alkoxycarbonyl, carboxy- C_xH_{2x} -, hydroxy, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino or



, or R^{17} and

R^{18} , together with the carbon atom, to which they are attached, form



R^{19} is selected from aminocarbonyl; aminosulfonyl; C_{1-6} alkoxycarbonyl- C_yH_{2y} -; C_{1-6} alkyl, which is unsubstituted or substituted by fluoro; C_{1-6} alkylaminosulfonyl; C_{1-6} alkylcarbonyl; and

10 hydroxy- C_xH_{2x} -carbonyl;

A is C_{1-6} alkylpyrazolyl;

x is 1-6;

y is 0-6;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers

15 thereof.

Further embodiment of present invention is (xxiv) a compound of formula IC, wherein

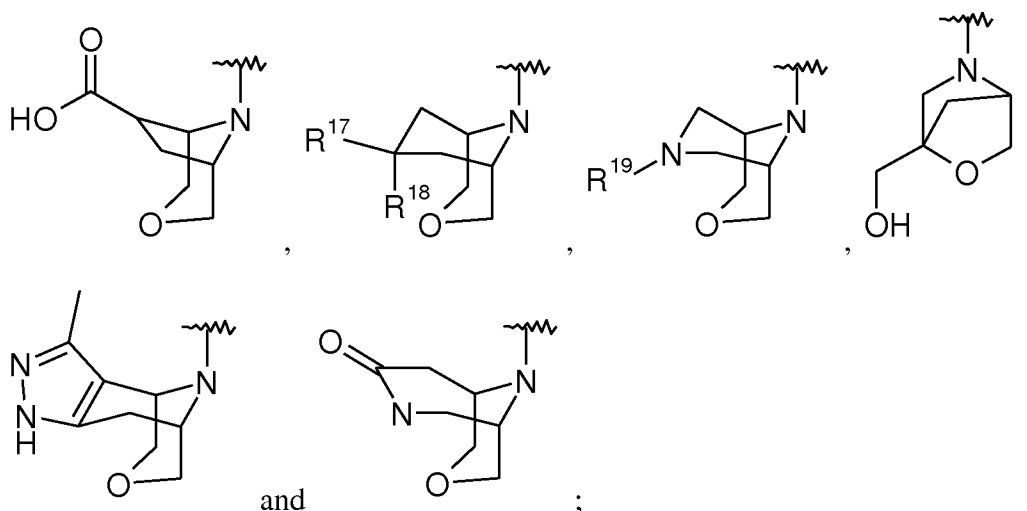
R^1 is methyl or ethyl;

R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro or bromo;

20 R^3 is hydrogen;

R^4 is selected from

-35-



wherein R^{17} is hydrogen;

R^{18} is methoxycarbonyl, methoxycarbonylmethyl(hydroxy), carboxymethyl, hydroxy,
5 methylcarbonylamino or methylsulfonylamino;

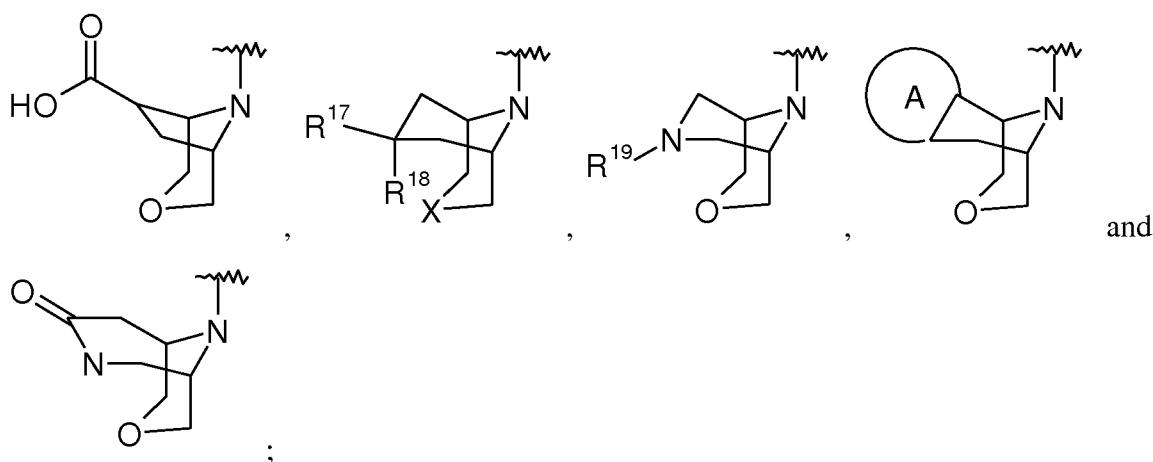
or R^{17} and R^{18} , together with the carbon atom, to which they are attached, form  ;

R^{19} is aminocarbonyl, aminosulfonyl, methoxycarbonyl, ethoxycarbonylisopropyl, methyl,
difluoroethyl, methylaminosulfonyl, methylcarbonyl, or hydroxymethylcarbonyl;
or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers
10 thereof.

Another embodiment of present invention is (xxv) a compound of formula IC or a
pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers
thereof, wherein

- 15 R^1 is C_{1-6} alkyl;
 R^2 is phenyl, which is once or twice or three times substituted by halogen;
 R^3 is hydrogen or C_{1-6} alkyl;
 R^4 is selected from

-36-



X is -O- or -S-; provided that

when X is -O-, R^{17} is hydrogen or hydroxy, R^{18} is C_{1-6} alkoxycarbonyl- C_yH_{2y} -, carboxy-
 5 C_yH_{2y} -, hydroxy- C_yH_{2y} -, C_{1-6} alkylcarbonyl-O-, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino

C_{1-6} alkoxycarbonyl- C_xH_{2x} -
 or $\begin{array}{c} \text{OH} \\ | \\ \text{C}_x\text{H}_{2x} \end{array}$, or R^{17} and R^{18} , together with the carbon atom, to which

they are attached, form $\begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{N} \end{array}$;

when X is -S-, R^{17} is hydrogen, R^{18} is carboxy- C_yH_{2y} -;

R^{19} is selected from aminocarbonyl; aminosulfonyl; C_{1-6} alkoxycarbonyl- C_yH_{2y} -; C_{1-6} alkyl,
 10 which is unsubstituted or substituted by fluoro; C_{1-6} alkylaminosulfonyl; C_{1-6} alkylcarbonyl; C_{1-6} alkylsulfonyl and hydroxy- C_xH_{2x} -carbonyl;

A is pyrazolyl or oxypyrazolyl, which is unsubstituted or substituted by C_{1-6} alkyl;

x is 1-6;

y is 0-6.

15

Further embodiment of present invention is (xxvi) a compound of formula IC or a
 pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers
 thereof, wherein

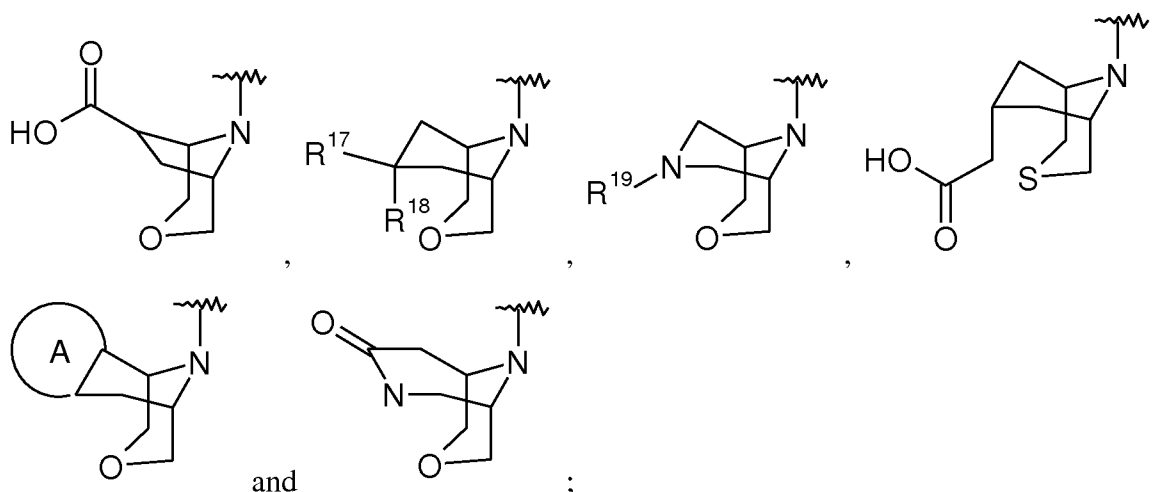
R^1 is methyl or ethyl;

20 R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro or bromo;

R^3 is hydrogen or methyl;

R^4 is selected from

-37-



R^{17} is hydrogen or hydroxy;

R^{18} is methoxycarbonyl, methoxycarbonylmethyl, methoxycarbonylmethyl(hydroxy),
 5 carboxy, carboxymethyl, hydroxy, hydroxymethyl, methylcarbonyl-O-, methylcarbonylamino or
 methylsulfonylamino;

or R^{17} and R^{18} , together with the carbon atom, to which they are attached, form  ;

R^{19} is aminocarbonyl, aminosulfonyl, methoxycarbonyl, ethoxycarbonylisopropyl, methyl,
 isopropyl, difluoroethyl, methylaminosulfonyl, methylcarbonyl, methylsulfonyl or
 10 hydroxymethylcarbonyl;

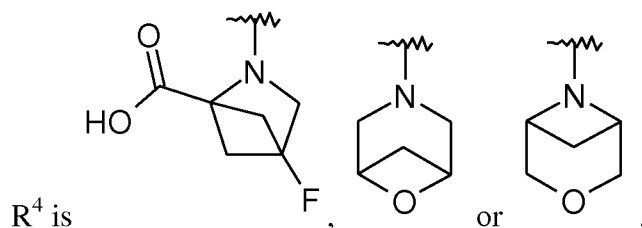
A is pyrazolyl or oxypyrazolyl, which is unsubstituted or substituted by methyl.

Another embodiment of present invention is (xxvii) a compound of formula IC or a
 pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers
 15 thereof, wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen;

R^3 is hydrogen;

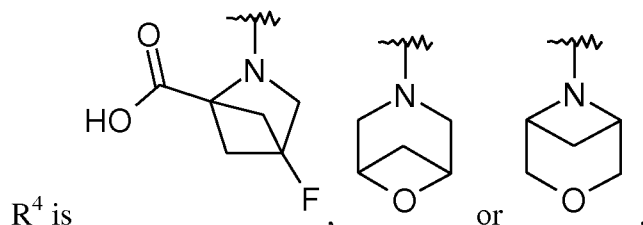


Further embodiment of present invention is (xxviii) a compound of formula IC or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof, wherein

R^1 is methyl;

5 R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro or bromo;

R^3 is hydrogen;



10 Particular compounds of formula I, including their activity data, NMR data and MS data are summarized in the following Table 1 and 2.

Particular compounds of formula I include the following:

9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid;

15 9-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-(4-methyl-thiazol-2-yl)-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid;

9-[6-(3,4-Difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid;

9-[(R)-6-(2-Bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester;

20 9-[(R)-6-(2-Bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid;

8-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-8-aza-bicyclo[3.2.1]octane-6-carboxylic acid;

25 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-hydroxy-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Acetoxy-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-hydroxy-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-hydroxy-7-hydroxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

5 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methanesulfonyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

10 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-isopropyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(2,2-difluoro-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

15 (R)-6-(7-Acetyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methylsulfamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

20 9-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester;

(R)-6-(7-Carbamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-sulfamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

25 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(1-ethoxycarbonyl-1-methyl-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

30 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(2-hydroxy-acetyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

7-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester;

(S)-2-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-5,5-difluoro-2-aza-bicyclo[2.2.2]octane-3-carboxylic acid;

(R)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

5 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methoxycarbonylmethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid ethyl ester;

10 6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(3,4-difluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Bromo-4-fluoro-phenyl)-6-(7-carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

15 (S)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(3,4-difluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid ethyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(hydroxy-methoxycarbonyl-methyl)-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

20 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(3-methyl-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

25 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(5-methyl-3-oxo-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodec-2(6)-en-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(4-oxo-8-oxa-3,10-diaza-bicyclo[4.3.1]dec-10-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

30 (R)-6-(7-Acetylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methanesulfonylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(2-methoxymethyl-azetidin-1-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(6-oxa-3-aza-bicyclo[3.1.1]hept-3-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

5 (S)-3-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3,6-diaza-bicyclo[3.2.1]octane-7-carboxylic acid;

2-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-4-fluoro-2-aza-bicyclo[2.1.1]hexane-1-carboxylic acid;

10 (R)-6-(5-Acetyl-2,5-diaza-bicyclo[2.2.1]hept-2-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

6-(7-Carboxymethyl-3-thia-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Diazirine-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

15 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-((1R,3R,5S)-3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(9-oxa-3,4,11-triaza-tricyclo[5.3.1.0*2,6*]undeca-2(6),4-dien-11-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

20 2-[[[(1R,5S)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]oxy]acetic acid;

2-[[[(1R,5S)-9-[[[(4S)-4-(3,4-difluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]oxy]acetic acid;

Methyl (4R)-6-[(6-acetamido-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

25 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-hydroxy-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

2-[[[8-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]oxy]acetic acid;

30 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-fluoro-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

8-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-6-carboxylic acid;

Methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-[[7-(2-hydroxyacetyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-[(7-carbamoyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

5 2-[(1R,5S)-9-[[4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(1R,5S)-7-endo-(sulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

10 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-6-[(1S,5R)-7-endo-ureido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-1,4-dihydropyrimidine-5-carboxylate;

2-[(1S,5R)-9-[[4-(2-bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

15 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(1R,5S)-7-exo-(methanesulfonamido)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-6-[(1S,5R)-7-exo-acetamido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

20 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-6-[(1S,5R)-7-exo-ureido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(1R,5S)-7-exo-(sulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

2-[(1R,5S,6S)-8-[[4-(2-bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]acetic acid;

25 Endo-2-[(1S,5R)-9-[[4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

30 Exo-2-[(1S,5R)-9-[[4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[4-(2-bromo-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Ethyl (4R)-6-[[[(1S,5R)-7-endo-acetamido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-bromo-4-fluoro-phenyl)-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate;

5 Ethyl (4R)-6-[[[(1S,5R)-7-exo-acetamido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-bromo-4-fluoro-phenyl)-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

10 Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromo-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2,3-difluorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

15 Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromophenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

20 Exo-2-[(1S,5R)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

3-[(1S,5R)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl]-2,2-dimethyl-3-oxo-propanoic acid;

25 Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromo-3,4-difluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

(1S,5R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

(1R,5S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

30 8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

(1S,5R)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

(1R,5S)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

5 2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

10 2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chlorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chlorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

15 2-[(1R,3S,5S)-8-[[[(4R)-4-(2-bromophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[[(4R)-4-(2-bromophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

20 2-[(1R, 3S,5S)-8-[[[(4R)-4-(2-bromo-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S, 3R,5R)-8-[[[(4R)-4-(2-bromo-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

25 2-[(1S,3R,5R)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

30 2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,5S,6R,7R)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(1R,5R,6S,7S)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(1S,5S,6R,7R)-9-[[[(4R)-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

5 2-[(1R,5R,6S,7S)-9-[[[(4R)-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

(4R)-4-(2-Chloro-4-fluoro-phenyl)-6-(4,10-dioxa-5,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2,5-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

10 (4R)-4-(2-Chloro-4-fluoro-phenyl)-6-(5,10-dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(4R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-fluoro-5,10-dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester;

15 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7,7-difluoro-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

Methyl (4R)-4-(2-chloro-4-fluorophenyl)-6-[(6,6-difluoro-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-(1,3-thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate;

20 2-[(1R,3R,5S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3S,5R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3R,5S)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

25 2-[(1S,3S,5R)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3R,5S)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid or 2-

30 [(1S,3S,5R)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[[(4S)-4-(3,4-difluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[[(4S)-4-(3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

5 2-[(3S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3R)-8-[[[(4R)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic
10 acid;

2-[(3S)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3R)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic
15 acid;

2-[(3S)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

20 Methyl (4R)-6-[(3-acetyl-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

2-[(7S)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7R)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;
25

2-[(7R)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7S)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

30 2-[(7R)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7S)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7R)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7S)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

5 2-[(1R,5R,7S)-9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid or 2-[(1S,5S,7R)-9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

10 2-[(1R,5R,7S)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid or 2-[(1S,5S,7R)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

15 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Endo-2-[9-[[[(4R)-4-(2-bromophenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

20 Endo-2-[9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Endo-2-[9-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

25 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-1-hydroxy-2-oxo-ethyl)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-6,7-dihydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

7-amino-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid;

30 7-amino-9-[[[(4R)-4-(2,3-difluorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid;

7-amino-9-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(8-oxa-3-azabicyclo[3.2.1]octan-3-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

5 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(5,5-difluoro-3-azabicyclo[2.2.1]heptan-3-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-6-[[4-(acetamidomethyl)-5-oxa-2-azabicyclo[2.2.1]heptan-2-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

10 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-7-(methanesulfonamido)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-7-[(2,2,2-trifluoroacetyl)amino]-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

15 (1S,4R)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylic acid;

(1R,4S)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylic acid;

20 8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

(5S)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-5-carboxylic acid; and
(5R)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-5-carboxylic acid.

25

Table 1: NMR and MS data of particular compounds

Example No.	¹ H NMR data	MW data
1	¹ H NMR (CDCl ₃ , 400 MHz): 10.0 (br s, 1H), 7.88 (d, J = 3.0 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.27 (m, 1H), 7.15 (dd, J = 2.4, 8.5 Hz, 1H), 6.94 (m, 1H), 6.22 (s, 1H), 4.50 (m, 2H), 4.23 (s, 2H), 3.95 (m, 2H), 3.85 (m, 1H), 3.63 (s, 3H), 2.83 (m, 2H), 2.33 (m, 2H), 2.05 (m, 2H).	LC/MS: calc'd 535 (MH ⁺), exp 535 (MH ⁺)

2	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.41 (dd, J = 8.7, 6.1 Hz, 1H), 7.32 (d, J = 1 Hz, 1H), 7.24 (dd, J = 8.8, 2.8 Hz, 1H), 7.04 (m, 1H), 6.16 (s, 1H), 4.62 (d, J = 17.8 Hz, 1H), 4.08 - 4.23 (m, 3H), 3.92 (m, 2H), 3.71 (m, 1H), 3.63 (s, 3H), 2.88 (m, 1H), 2.83 (m, 1H), 2.49 (d, J = 0.8 Hz, 3H), 2.30 (m, 2H), 2.04 (m, 2 H).	LC/MS: calc'd 549 (MH ⁺), exp 549 (MH ⁺)
3	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.01 (d, J = 3.3 Hz, 1H), 7.80 (d, J = 3.3Hz, 1H), 7.13 - 7.27 (m, 3H), 5.73 (s, 1H), 4.54 (d, J = 17.8 Hz, 1H), 4.14 (m, 2H), 4.01 (d, J = 17.8 Hz, 1H), 3.81 - 3.96 (m, 2H), 3.72 (s, 3H), 3.64 (m, 1H), 2.78 (m, 1H), 2.68 (m, 1H), 2.22 (m, 2H), 1.93 (m, 2 H).	LC/MS: calc'd 519 (MH ⁺), exp 519 (MH ⁺)
4	¹ H NMR (DMSO-d ₆ , 400 MHz): 9.84 - 10.20 (m, 1H), 7.99 - 8.07 (m, 1H), 7.95 (d, J = 3.3 Hz, 1H), 7.57 (dd, J = 8.7, 2.64 Hz, 1H), 7.39 (dd, J = 8.7, 6.15 Hz, 1H), 7.20 (td, J = 8.5, 2.64 Hz, 1H), 6.02 (s, 1H) 4.35 (d, J = 17.6 Hz, 1H), 4.02 - 4.13 (m, 1H), 3.79 - 3.98 (m, 4H), 3.64 (s, 3H), 3.59 (t, J = 5.8 Hz, 1H), 3.53 (s, 3H), 2.82 (m, 1H), 2.64 - 2.72 (m, 1H), 1.95 - 2.13 (m, 2H), 1.83 (td, J = 13.2, 5.1 Hz, 2 H).	LC/MS: calc'd 593&595 (MH ⁺), exp 593&595 (MH ⁺)
5	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.96 (d, J = 3.3 Hz, 1H), 7.75 (d, J = 3.0 Hz, 1H), 7.35 - 7.47 (m, 2H), 7.09 (td, J = 8.4, 2.8 Hz, 1H), 6.16 (s, 1H), 4.56 (d, J = 17.6 Hz, 1H), 4.04 - 4.21 (m, 3H), 3.86 - 3.97 (m, 2H), 3.65 - 3.74 (m, 1H), 3.60 (s, 3H), 2.84 (m, 1H), 2.73 (m, 1H), 2.25 (d, J = 12.3 Hz, 2H), 1.89 - 2.03 (m, 2 H).	LC/MS: calc'd 579&581 (MH ⁺), exp 579&581 (MH ⁺)
6	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.1 Hz, 0.5H), 7.97 (d, J = 3.1 Hz, 0.5H), 7.77 (d, J = 3.0 Hz, 1H), 7.44 (m, 1H), 7.24 (dd, J = 8.8, 2.8 Hz, 1H), 7.06 (td, J = 8.4, 2.8 Hz, 1H), 6.18 (s, 0.5H), 6.18 (s, 0.5H), 4.20 (m, 1H), 3.88-4.07 (m, 4H), 3.68 (m, 1H), 3.61 (s, 3H), 3.47 (m, 2H), 3.31 (m, 1H), 2.48 (m, 1H), 2.36 (m, 1H).	LC/MS: calc'd 521 (MH ⁺), exp 521 (MH ⁺)
7	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.3 Hz, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.41 (dd, J = 8.7, 6.1 Hz, 1H), 7.24 (dd, J = 8.8, 2.8 Hz, 1H), 7.04 (td, J = 8.4, 2.8 Hz, 1H),	LC/MS: calc'd 507 (MH ⁺), exp 507 (MH ⁺)

	6.17 (s, 1H), 4.52 (d, J = 17.8 Hz, 1H), 4.04 - 4.16 (m, 4H), 3.86 (m, 2H), 3.62 (s, 3H), 2.86 (m, 1H), 2.77 (m, 1H), 2.49 (m, 2H), 1.73 (m, 2 H).	
8	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.0 Hz, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.41 (dd, J = 8.7, 6.1 Hz, 1H), 7.24 (dd, J = 8.8, 2.5 Hz, 1H), 7.04 (td, J = 8.4, 2.5 Hz, 1H), 6.18 (s, 1H), 5.86 (m, 1H), 4.53 (d, J = 17.8 Hz, 1H), 4.08 (d, J = 17.8 Hz, 1H), 4.04 (m, 2H), 3.86 (dd, J = 18.3, 11.0 Hz, 2H), 3.63 (s, 3H), 2.96 (m, 1H), 2.83 (m, 1H), 2.07 (s, 3H), 2.05 (m, 4H).	LC/MS: calc'd 549 (MH ⁺), exp 549 (MH ⁺)
9	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (d, J = 3.0 Hz, 1H), 7.75 (d, J = 3.3 Hz, 1H), 7.41 (dd, J = 8.7, 6.1 Hz, 1H), 7.23 (dd, J = 8.7, 2.6 Hz, 1H), 7.04 (td, J = 8.4, 2.8 Hz, 1H), 6.17 (s, 1H), 4.73 (m, 1H), 4.49 (d, J = 17.8 Hz, 1H), 3.97 - 4.14 (m, 3H), 3.82 (dd, J = 17.8, 11.0 Hz, 2H), 3.63 (s, 3H), 2.91 (m, 1H), 2.79 (m, 1H), 1.84 - 2.09 (m, 4 H).	LC/MS: calc'd 507 (MH ⁺), exp 507 (MH ⁺)
10	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.87 (d, J = 3.2 Hz, 1H), 7.75 (d, J = 3.1 Hz, 1H), 7.42 (m, 1H), 7.24 (m, 1H), 7.06 (m, 1H), 6.18 (s, 1H), 4.54 (d, J = 14.6, 1H), 4.12 (d, J = 13.0, 1H), 4.04 (m, 1H), 3.88 (s, 2H), 3.70 (m, 2H), 3.63 (s, 3H), 2.84 (m, 2H), 2.14 (m, 2H), 1.98 (m, 2H).	LC/MS: calc'd 537 (MH ⁺), exp 537 (MH ⁺)
11	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (d, J = 3.0 Hz, 1H), 7.77 (d, J = 3.3 Hz, 1H), 7.43 (dd, J = 8.8, 6.0 Hz, 1H), 7.24 (dd, J = 8.8, 2.8 Hz, 1H), 7.05 (td, J = 8.4, 2.8 Hz, 1H), 6.18 (s, 1H), 4.68 (d, J = 17.3 Hz, 1H), 4.16 - 4.22 (m, 3H), 3.95 (m, 2H), 3.73 (m, 2H), 3.63 (s, 3H), 3.54 (m, 2H), 2.94 (s, 3H), 2.86 (m, 2 H).	LC/MS: calc'd 570 (MH ⁺), exp 570 (MH ⁺)
12	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.18 (d, J = 3.3 Hz, 1H), 8.10 (d, J = 3.0 Hz, 1H), 7.56 (dd, J = 8.8, 6.0 Hz, 1H), 7.34 (dd, J = 8.7, 2.6 Hz, 1H), 7.15 (td, J = 8.3, 2.6 Hz, 1H), 6.28 (s, 1H), 4.56 (d, J = 16.1 Hz, 1H), 4.20 (m, 3H), 4.10 (m, 2H), 3.72 (m, 1H), 3.68 (m, 1H), 3.67 (s, 3H), 3.54 - 3.61 (m, 2H), 3.16 (m, 2H), 2.95 (s, 3 H).	LC/MS: calc'd 506 (MH ⁺), exp 506 (MH ⁺)

13	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.96 (d, J = 3.0 Hz, 1H), 7.77 (d, J = 3.3 Hz, 1H), 7.41 (dd, J = 8.7, 6.1 Hz, 1H), 7.24 (dd, J = 8.8, 2.8 Hz, 1H), 7.05 (td, J = 8.5, 2.6 Hz, 1H), 6.18 (s, 1H), 4.62 (d, J = 18.1 Hz, 1H), 4.09 - 4.21 (m, 3H), 3.91 (m, 2H), 3.63 (s, 3H), 3.02 (m, 4H), 2.79 (m, 2H), 2.70 (m, 1H), 1.20 (d, J = 5.8 Hz, 6 H).	LC/MS: calc'd 534 (MH ⁺), exp 534 (MH ⁺)
14	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.09 (d, J = 3.0 Hz, 1H), 7.97 (d, J = 3.0 Hz, 1H), 7.52 (dd, J = 8.8, 6.0 Hz, 2H), 7.31 (dd, J = 8.5, 2.5 Hz, 1H), 7.11 (td, J = 8.3, 2.6 Hz, 1H), 6.47 (m, 1H), 6.24 (s, 1H), 4.65 (d, J = 16.3 Hz, 1H), 4.30 (d, J = 16.3 Hz, 1H), 4.23 (m, 2H), 4.15 (m, 2H), 3.72 (m, 4H), 3.66 (s, 3H), 3.64 (m, 2H), 3.30 (m, 2H).	LC/MS: calc'd 556 (MH ⁺), exp 556 (MH ⁺)
15	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.02 - 8.09 (m, 1H), 7.97 (d, J = 3.0 Hz, 1H), 7.57 (dd, J = 8.7, 5.9 Hz, 1H), 7.31 (dd, J = 8.7, 2.6 Hz, 1H), 7.13 (td, J = 8.4, 2.5 Hz, 1H), 6.24 (s, 1H), 5.03 (dd, J = 16.9, 2.1 Hz, 1H), 4.91 (m, 1H), 4.68 (d, J = 16.8 Hz, 1H), 4.19 - 4.37 (m, 4H), 4.03 - 4.14 (m, 2H), 3.67 (s, 3H), 3.45 - 3.59 (m, 3H), 2.20 (d, J = 0.7 Hz, 3 H).	LC/MS: calc'd 534 (MH ⁺), exp 534 (MH ⁺)
16	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.07 (d, J = 3.3 Hz, 1H), 7.97 (d, J = 3.3 Hz, 1H), 7.56 (dd, J = 8.7, 5.9 Hz, 1H), 7.31 (dd, J = 8.7, 2.6 Hz, 1H), 7.13 (td, J = 8.4, 2.5 Hz, 1H), 6.24 (s, 1H), 4.98 (d, J = 17.1 Hz, 1H), 4.59 (d, J = 15.1 Hz, 1H), 4.31 (d, J = 12.8 Hz, 2H), 4.11 (d, J = 12.8 Hz, 2H), 3.84 (dd, J = 13.4, 6.40 Hz, 2H), 3.62 - 3.75 (m, 5H), 3.50 (d, J = 1.8 Hz, 2H), 2.72 (s, 3 H).	LC/MS: calc'd 585 (MH ⁺), exp 585 (MH ⁺)
17	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.3 Hz, 1H), 7.79 (d, J = 3.3 Hz, 1H), 7.44 (dd, J = 8.8, 6.0 Hz, 1H), 7.25 (dd, J = 8.7, 2.6 Hz, 1H), 7.06 (td, J = 8.4, 2.5 Hz, 1H), 6.19 (s, 1H), 4.72 (d, J = 17.3 Hz, 1H), 4.11 - 4.32 (m, 5H), 3.89 - 4.01 (m, 2H), 3.75 (s, 3H), 3.53 - 3.71 (m, 5H), 2.72 - 2.89 (m, 2 H).	LC/MS: calc'd 550 (MH ⁺), exp 550 (MH ⁺)
18	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.3 Hz, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.43 (dd, J = 8.8, 6.0 Hz, 1H),	LC/MS: calc'd 535 (MH ⁺), exp

	7.24 (dd, J = 8.8, 2.51 Hz, 1H), 7.05 (td, J = 8.4, 2.8 Hz, 1H), 6.18 (s, 1H), 4.67 (d, J = 17.6 Hz, 1H), 4.10 - 4.26 (m, 3H), 3.98 - 4.07 (m, 2H), 3.87 - 3.96 (m, 2H), 3.63 (s, 3H), 3.57 (m, 2H), 2.75 (d, J = 19.3 Hz, 2 H).	535 (MH ⁺)
19	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.92 - 8.03 (m, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.43 (dd, J = 8.7, 6.1 Hz, 1H), 7.24 (dd, J = 8.8, 2.5 Hz, 1H), 7.05 (td, J = 8.4, 2.8 Hz, 1H), 6.18 (s, 1H), 4.58 - 4.72 (m, 1H), 4.10 - 4.26 (m, 3H), 3.89 - 4.01 (m, 2H), 3.62 (s, 3H), 3.53 - 3.61 (m, 2H), 3.39 - 3.48 (m, 2H), 2.92 (m, 1H), 2.80 - 2.89 (m, 1 H).	LC/MS: calc'd 571 (MH ⁺), exp 571 (MH ⁺)
20	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (d, J = 3.0 Hz, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.41 (dd, J = 8.8, 6.0 Hz, 1H), 7.23 (dd, J = 8.8, 2.5 Hz, 1H), 7.04 (td, J = 8.4, 2.5 Hz, 1H), 6.15 - 6.20 (m, 1H), 4.62 (d, J = 17.8 Hz, 1H), 4.25 (q, J = 7.0 Hz, 2H), 4.11 - 4.20 (m, 3H), 3.87 (t, J = 10.9 Hz, 2H), 3.62 (s, 3H), 3.09 - 3.17 (m, 2H), 2.98 (d, J = 11.5 Hz, 2H), 2.71 - 2.81 (m, 2H), 1.40 (s, 6H), 1.35 (t, J = 7.1 Hz, 3 H).	LC/MS: calc'd 606 (MH ⁺), exp 606 (MH ⁺)
21	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (dd, J = 3.0, 1.8 Hz, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.43 (dd, J = 8.8, 6.0 Hz, 1H), 7.24 (dd, J = 8.7, 2.6 Hz, 1H), 7.01 - 7.09 (m, 1H), 6.18 (s, 1H), 4.69 (d, J = 17.6 Hz, 1H), 4.54 (d, J = 13.8 Hz, 1H), 4.18 - 4.36 (m, 3H), 4.15 (dt, J = 11.3, 2.5 Hz, 2H), 3.86 - 4.02 (m, 2H), 3.79 (d, J = 6.8 Hz, 2H), 3.63 (s, 3H), 3.44 (t, J = 11.2 Hz, 1H), 2.78 (t, J = 16.6 Hz, 2 H).	LC/MS: calc'd 550 (MH ⁺), exp 550 (MH ⁺)
22	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.00 (m, 1H), 7.72 (m, 1H), 7.45 (m, 1H), 7.25 (m, 1H), 7.10 (m, 1H), 6.17 (s, 1H), 4.60 (m, 1H), 3.75 - 4.16 (m, 6H), 3.45 (m, 1H), 3.62 (s, 3H), 3.06 (m, 2H), 2.77 (m, 2H), 1.37 (s, 9 H).	LC/MS: calc'd 592 (MH ⁺), exp 592 (MH ⁺)
23	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (d, J = 3.0 Hz, 1H), 7.87 (d, J = 2.8 Hz, 1H), 7.54 (dd, J = 8.7, 6.1 Hz, 1H), 7.27 (dd, J = 8.7, 2.6 Hz, 1H), 7.15 (td, J = 8.4, 2.5 Hz, 1H), 6.19 (s, 1H), 4.10 (m, 2H), 3.85 (m, 1H), 3.65 (s, 3H), 2.85 (m, 2H), 2.40 (m, 1H), 2.20 (m, 1H), 1.79 - 2.04 (m, 4 H).	LC/MS: calc'd 555 (MH ⁺), exp 555 (MH ⁺)

24	¹ H NMR (DMSO-d ₆ , DMSO-d ₆): 12.05 (brs., 1H), 10.04 (s, 1H), 8.00 (d, J = 3.3 Hz, 1H), 7.94 (d, J = 3.0 Hz, 1H), 7.34 - 7.48 (m, 2H), 7.16 (td, J = 8.5, 2.6 Hz, 1H), 6.04 (s, 1H), 4.34 (d, J = 18.1, 1H), 4.14 (d, J = 17.8 Hz, 1H), 3.80 (m, 2H), 3.53 (s, 3H), 3.44 (dd, J = 10.8, 3.5 Hz, 2H), 2.84 (m, 2H), 2.43 (m, 1H), 2.35 (m, 2H), 2.23 (m, 2H), 1.29 (m, 2 H).	LC/MS: calc'd 549 (MH ⁺), exp 549 (MH ⁺)
25	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.96 - 8.02 (m, 1H), 7.75 (d, J = 3.3 Hz, 1H), 7.41 (dd, J = 8.7, 6.1 Hz, 1H), 7.23 (dd, J = 8.8, 2.5 Hz, 1H), 7.04 (td, J = 8.4, 2.8 Hz, 1H), 6.17 (s, 1H), 4.47 - 4.59 (m, 1H), 4.14 (d, J = 17.8 Hz, 1H), 4.01 (ddd, J = 11.2, 7.4, 2.0 Hz, 2H), 3.69 (s, 3H), 3.61 (s, 3H), 3.45 - 3.55 (m, 2H), 2.84 (t, J = 8.5 Hz, 2H), 2.60 - 2.73 (m, 1H), 2.50 - 2.59 (m, 2H), 2.37 (dq, J = 14.3, 7.0 Hz, 2H), 1.38 - 1.51 (m, 2 H).	LC/MS: calc'd 563 (MH ⁺), exp 563 (MH ⁺)
26	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.89 - 8.03 (m, 1H), 7.73 - 7.83 (m, 1H), 7.49 (dd, J = 8.8, 6.0 Hz, 1H), 7.24 (dd, J = 8.7, 2.6 Hz, 1H), 7.07 (td, J = 8.4, 2.5 Hz, 1H), 6.11 - 6.24 (m, 1H), 4.72 (d, J = 17.6 Hz, 1H), 4.30 - 4.46 (m, 1H), 3.95 - 4.18 (m, 4H), 3.65 (dd, J = 11.8, 4.3 Hz, 2H), 3.11 - 3.27 (m, 2H), 2.60 - 2.73 (m, 1H), 2.42 - 2.60 (m, 4H), 1.52 - 1.70 (m, 2H), 1.03 - 1.26 (m, 3 H).	LC/MS: calc'd 563 (MH ⁺), exp 563 (MH ⁺)
27	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.07 (d, J = 3.0 Hz, 1H), 7.78 (d, J = 3.1 Hz, 1H), 7.12 - 7.26 (m, 3H), 5.72 (s, 1H), 4.52 (d, J = 18.1Hz, 1H), 4.05 (d, J = 18.1Hz, 1H), 3.99 (m, 2H), 3.72 (s, 3H), 3.52 (m, 2H), 2.82 (m, 2H), 2.56 (m, 1H), 2.28 - 2.43 (m, 4H), 1.43 (m, 2 H).	LC/MS: calc'd 533 (MH ⁺), exp 533 (MH ⁺)
28	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.99 (d, J = 3.0 Hz, 1H), 7.74 (d, J = 3.0 Hz, 1H), 7.33 - 7.49 (m, 2H), 7.09 (td, J = 8.4, 2.5 Hz, 1H), 6.11 - 6.19 (m, 1H), 4.56 (d, J = 17.8 Hz, 1H), 4.16 (d, J = 18.3 Hz, 1H), 3.96 - 4.08 (m, 2H), 3.65 (s, 3H), 3.53 (d, J = 11.5 Hz, 2H), 2.86 (m, 2H), 2.59 - 2.69 (m, 1H), 2.47 (d, J = 7.0 Hz, 2H), 2.42 (m, 2H), 1.39 - 1.54 (m, 2 H).	LC/MS: calc'd 593&595 (MH ⁺), exp 593&595 (MH ⁺)
29	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.03 (d, J = 3.1 Hz,	LC/MS: calc'd

	1H), 7.79 (d, J = 2.9 Hz, 1H), 7.12 - 7.28 (m, 3H), 5.73 (s, 1H), 4.57 (d, J = 19.4 Hz, 1H), 4.07 - 4.23 (m, 3H), 3.95 - 4.03 (m, 2H), 3.52 (d, J = 11.9 Hz, 2H), 2.76 - 2.88 (m, 2H), 2.59 - 2.68 (m, 1H), 2.46 (d, J = 7.1 Hz, 2H), 2.38 (m, 2H), 1.39 - 1.51 (m, 2H), 1.27 (t, J = 7.1 Hz, 3 H).	547 (MH ⁺), exp 547 (MH ⁺)
30	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.01 (d, J = 3.0 Hz, 1H), 7.75 (d, J = 3.0 Hz, 1H), 7.40 (dd, J = 8.5, 6.3 Hz, 1H), 7.23 (dd, J = 8.7, 2.6 Hz, 1H), 7.04 (td, J = 8.4, 2.0 Hz, 1H), 6.17 (d, J = 3.0 Hz, 1H), 4.44 - 4.63 (m, 1H), 4.32 - 4.40 (m, 1H), 4.07 - 4.23 (m, 1H), 3.94 - 4.05 (m, 2H), 3.76 (m, 3H), 3.63 (s, 3H), 3.47 - 3.59 (m, 2H), 2.77 - 2.95 (m, 2H), 2.48 - 2.65 (m, 1H), 2.11 - 2.27 (m, 2H), 1.83 (d, J = 2.5 Hz, 1H), 1.70 (m, 1 H).	LC/MS: calc'd 579 (MH ⁺), exp 579 (MH ⁺)
31	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.04 (d, J = 3.1 Hz, 0.5H), 8.03 (d, J = 3.1 Hz, 0.5H), 7.95 (d, J = 3.0 Hz, 0.5H), 7.94 (d, J = 3.0Hz, 0.5H), 7.71 (s, 0.5H), 7.66 (s, 0.5H), 7.53 (m, 1H), 7.29 (m, 1H), 7.12 (m, 1H), 6.18 (s, 1H), 5.08 (s, 0.5H), 4.95 (s, 0.5H) 4.71 (m, 1H), 4.46 (m, 0.5H), 4.42 (m, 0.5H), 4.19-4.34 (m, 3H), 4.12 (m, 1H), 3.90 (m, 1H), 3.57 (s, 1.5H), 3.55 (s, 1.5H), 3.53 (m, 1H), 3.26 (m, 1H).	LC/MS: calc'd 529 (MH ⁺), exp 529 (MH ⁺)
32	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.00 (m, 1H), 7.77 (m, 1H), 7.44 (m, 1H), 7.25 (m, 1H), 7.07 (m, 1H), 6.17 (s, 0.5H), 6.15 (s, 0.5H), 4.11 (m, 3H), 3.85 (m, 3H), 3.79 (m, 2H), 3.52 (s, 1.5H), 3.50 (s, 1.5H), 3.20 (m, 1H), 2.71 (m, 1H), 2.24 (s, 1.5H), 2.18 (s, 1.5H).	LC/MS: calc'd 543 (MH ⁺), exp 543 (MH ⁺)
33	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.00 (m, 1H), 7.77 (m, 1H), 7.44 (m, 1H), 7.25 (m, 1H), 7.07 (m, 1H), 6.18 (s, 0.5H), 6.15 (s, 0.5H), 4.11 (m, 3H), 3.90 (m, 2H), 3.61 (m, 7H), 3.28 (m, 1H), 3.05 (m, 2H), 2.60 (m, 1H).	LC/MS: calc'd 559 (MH ⁺), exp 559 (MH ⁺)
34	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.0 Hz, 0.5H), 7.97 (d, J = 3.0Hz, 0.5H), 7.76 (d, J = 3.3 Hz, 1H), 7.42 (dd, J = 8.7, 6.1 Hz, 0.5H), 7.41 (dd, J = 8.7, 6.1 Hz, 0.5H), 7.24 (dd, J = 8.8, 2.8 Hz, 1H), 7.04 (m, 1H), 6.19 (s, 0.5H), 6.18	LC/MS: calc'd 520 (MH ⁺), exp 520 (MH ⁺)

	(s, 0.5H), 4.71 (d, J = 17.6Hz, 0.5H), 4.64 (d, J = 17.6Hz, 0.5H), 4.23 (d, J = 17.6Hz, 0.5H), 4.21 (d, J = 17.6Hz, 0.5H), 4.08 (m, 2H), 3.85-4.0 (m, 3H), 3.63 (s, 3H), 3.26 (m, 2H), 2.70-3.00 (m, 2H), 2.49 (m, 1H).	
35	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.99 (d, J = 3.0 Hz, 1H), 7.76 (d, J = 3.3 Hz, 1H), 7.40 (dd, J = 8.7, 6.1 Hz, 1H), 7.24 (dd, J = 8.8, 2.6 Hz, 1H), 6.99 - 7.10 (m, 1H), 6.17 (s, 1H), 4.55 (d, J = 17.8 Hz, 1H), 4.46 (m, 1H), 4.04 - 4.19 (m, 3H), 3.86 (m, 2H), 3.63 (s, 3H), 2.80 (m, 1H), 2.74 (m, 1H), 2.52 (m, 2H), 1.59 (m, 2 H).	LC/MS: calc'd 538 (MH ⁺), exp 538 (MH ⁺)
36	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.99 (d, J = 3.0 Hz, 1H), 7.76 (d, J = 3.3 Hz, 1H), 7.41 (dd, J = 8.7, 6.1 Hz, 1H), 7.23 (dd, J = 8.8, 2.5 Hz, 1H), 7.04 (td, J = 8.4, 2.8 Hz, 1H), 6.17 (s, 1H), 4.53 (d, J = 17.6 Hz, 1H), 4.14 (m, 2H), 4.08 (d, J = 17.6 Hz, 1H), 3.72 - 3.96 (m, 3H), 3.63 (s, 3H), 3.02 (s, 3H), 2.82 (m, 1H), 2.75 (m, 1H), 2.58 (m, 2H), 1.78 (m, 2 H).	LC/MS: calc'd 584 (MH ⁺), exp 584 (MH ⁺)
37	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.96 (d, J = 3.0 Hz, 1H), 7.75 (d, J = 3.3 Hz, 1H), 7.34 - 7.44 (m, 1H), 7.23 (dd, J = 8.8, 2.3 Hz, 1H), 6.97 - 7.09 (m, 1H), 6.16 (s, 1H), 4.13 - 4.46 (m, 4H), 3.79 - 3.93 (m, 2H), 3.63 (s, 3H), 3.57 (m, 1H), 3.34 - 3.39 (m, 1H), 2.91 (m, 1H), 1.96 (d, J = 8.5 Hz, 1 H).	LC/MS: calc'd 463 (MH ⁺), exp 463 (MH ⁺)
38	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.01 (d, J = 3.0 Hz, 1H), 7.90 (d, J = 3.0 Hz, 1H), 7.55 (dd, J = 8.5, 6.0 Hz, 1H), 7.30 (dd, J = 8.7, 2.4 Hz, 1H), 7.13 (td, J = 8.3, 2.5 Hz, 1H), 6.21 (s, 1H), 4.89-4.83 (m, 1H), 4.81-4.69 (m, 3H), 4.10 (d, J = 12.8 Hz, 1H), 4.01 (d, J = 12.8 Hz, 1H), 3.94-3.78 (m, 2H), 3.68 (s, 3H), 3.55-3.43 (m, 1H), 2.36 (d, J = 10.3 Hz, 1 H).	LC/MS: calc'd (MH ⁺) 463 exp (MH ⁺) 463.
39	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (s, 1H), 7.75 (s, 1H), 7.51 (m, 1H), 7.28 (m, 1H), 7.12 (m, 1H), 6.19 (s, 1H), 4.35~4.15 (m, 3H), 3.8~3.92 (m, 3H), 3.60 (s, 3H), 3.59 (1H, m), 3.10 (m, 1H), 2.80 (m, 1H), 2.05 (m, 1H), 1.85 (m, 1H).	LC/MS: calc'd 493 (MH ⁺), exp 493 (MH ⁺)
40	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.00 (d, J = 3.0 Hz, 1H), 7.90 (d, J = 3.3 Hz, 1H), 7.56 (dd, J = 8.5, 6.0 Hz, 1H),	LC/MS: calc'd 509 (MH ⁺), exp

	7.29 (dd, J = 8.5, 2.5 Hz, 1H), 7.12 (td, J = 8.3, 2.6 Hz, 1H), 6.20 (s, 1H), 4.99 (m, 1H), 3.88 (m, 1H), 3.63 (s, 3H), 3.37 (s, 2H), 2.74 (d, J = 7.8 Hz, 4 H).	509 (MH ⁺)
41	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.99 (m, 1H), 7.76 - 7.90 (m, 1H), 7.41 - 7.53 (m, 1H), 7.20 - 7.31 (m, 1H), 7.01 - 7.15 (m, 1H), 6.16 (s, 1H), 4.17 - 4.82 (m, 3H), 3.74 - 4.11 (m, 3H), 3.37 - 3.72 (m, 5H), 1.85 - 2.52 (m, 5 H).	LC/MS: calc'd 504 (MH ⁺), exp 504 (MH ⁺)
42	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.95 - 8.03 (m, 1H), 7.76 (d, J = 3.3 Hz, 1H), 7.41 (dd, J = 8.8, 6.3 Hz, 1H), 7.24 (dd, J = 8.8, 2.5 Hz, 1H), 7.05 (td, J = 8.4, 2.5 Hz, 1H), 6.17 (s, 1H), 4.56 (d, J = 17.8 Hz, 1H), 3.96 - 4.13 (m, 2H), 3.64 (s, 3H), 3.46 - 3.60 (m, 2H), 3.05 - 3.18 (m, 2H), 2.37 - 2.50 (m, 2H), 2.22 (d, J = 7.0 Hz, 2H), 1.95 - 2.05 (m, 2H), 1.80 - 1.95 (m, 2 H).	LC/MS: calc'd 565 (MH ⁺), exp 565 (MH ⁺)
43	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.00 (d, J = 3.2 Hz, 1H), 7.77 (d, J = 3.2 Hz, 1H), 7.43 (dd, J = 8.8, 6.0 Hz, 1H), 7.25 (dd, J = 8.8, 2.8 Hz, 1H), 7.05 (td, J = 8.4, 2.8 Hz, 1H), 6.19 (s, 1H), 4.63 (d, J = 17.2 Hz, 1H), 4.15 (m, 3H), 3.89 (m, 2H), 3.65 (s, 3H), 2.89 (m, 2H), 2.44 (td, J = 14.0, 5.0 Hz, 2H), 0.60 (m, 2H).	LC/MS: calc'd 517 (MH ⁺), exp 517 (MH ⁺)
44	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.01 (d, J = 3.2 Hz, 1H), 7.90 (d, J = 3.2 Hz, 1H), 7.55 (dd, J = 8.8, 6 Hz, 1H), 7.31 (d, J = 8.8, 2.4 Hz, 1H), 7.12 (td, J = 8.3, 2.6 Hz, 1H), 6.20 (s, 1H), 4.65 (d, J = 16.6 Hz, 1H), 4.43 (d, J = 16.6 Hz, 1H), 4.19 (m, 2H), 4.08 (m, 1H), 3.64 (s, 3H), 2.67 (m, 2H), 2.53 (m, 2H), 2.32 (m, 2H), 2.21 (m, 2 H).	LC/MS: calc'd 491 (MH ⁺), exp 491 (MH ⁺)
45	¹ H NMR (METHANOL-d ₄ , 400MHz): 8.01 (d, J = 3.0 Hz, 1H), 7.78 (d, J = 3.3 Hz, 1H), 7.39-7.49 (m, 2H), 7.23 (dd, J = 8.7, 2.6 Hz, 1H), 7.06 (td, J = 8.4, 2.8 Hz, 1H), 6.17 (s, 1H), 3.85-4.24 (m, 5H), 3.58-3.85 (m, 3H), 3.51 (s, 3H).	LC/MS: calc'd 515 (MH ⁺), exp 515 (MH ⁺)
46	¹ H NMR (METHANOL-d ₄ , 400MHz): 8.02 (d, J = 3.0 Hz, 1H), 7.81 (d, J = 3.0 Hz, 1H), 7.08-7.34 (m, 3H), 5.72 (s, 1H), 4.54 (d, J = 17.6 Hz, 1H), 4.17 (s, 2H), 3.94-4.12 (m, 4H), 3.71 (s,	LC/MS: calc'd 549 (MH ⁺), exp 549 (MH ⁺)

	3H), 3.70 (2H, m), 2.76-2.93 (m, 2H), 2.47 (m, 2H), 1.86(m, 2H).	
47	¹ H NMR (METHANOL-d ₄ , 400MHz): 8.02 (d, J = 3.0 Hz, 1H), 7.81 (d, J = 3.0 Hz, 1H), 7.08-7.34 (m, 3H), 5.72 (s, 1H), 4.54 (d, J = 17.6 Hz, 1H), 4.17 (s, 2H), 3.94-4.12 (m, 4H), 3.71 (s, 3H), 3.70 (2H, m), 2.76-2.93 (m, 2H), 2.47 (m, 2H), 1.86(m, 2H).	LC/MS: calc'd 549 (MH ⁺), exp 549 (MH ⁺)
48	¹ H NMR (METHANOL-d ₄ , 400MHz): 7.97 (d, J = 3.3 Hz, 1H), 7.76 (d, J = 3.3 Hz, 1H), 7.43 (m, 1H), 7.23 (dd, J = 8.7, 2.6 Hz, 1H), 7.06 (td, J = 8.4, 2.4 Hz, 0.5H), 7.05 (td, J = 8.4, 2.4 Hz, 0.5H), 6.17 (s, 1H), 4.68 (m, 1H), 4.17 (m, 1H), 3.63-4.09 (m, 5H), 3.61 (s, 3H), 3.30 (m, 0.5H), 3.20 (m, 1H), 3.08 (m, 0.5H), 2.63 (m, 1H), 2.03 (s, 1.5H), 2.02 (s, 1.5H), 1.85 (m, 1H).	LC/MS: calc'd 534 (MH ⁺), exp 534 (MH ⁺)
49	¹ H NMR (METHANOL-d ₄ , 400MHz): 7.98 (d, J = 3.1 Hz, 0.5H), 7.97 (d, J = 3.1 Hz, 0.5H), 7.77 (d, J = 3.1 Hz, 1H), 7.44 (dd, J = 8.7, 6.1 Hz, 0.5H), 7.43 (dd, J = 8.7, 6.1 Hz, 0.5H), 7.24 (dd, J = 8.8, 2.8 Hz, 1H), 7.06 (tt, J = 8.4, 2.8 Hz, 1H), 6.18 (s, 1H), 4.66 (m, 1H), 4.51 (m, 1H), 4.20 (m, 1H), 3.71-3.98 (m, 3H), 3.61 (s, 1.5H), 3.60 (s, 1.5H), 3.48-3.59 (m, 1H), 3.19 (m, 1H), 3.09 (m, 1H), 2.40 (m, 1H), 2.12 (m, 1H).	LC/MS: calc'd 493 (MH ⁺), exp 493 (MH ⁺)
50	¹ H NMR (METHANOL-d ₄ , 400MHz): 7.98 (d, J = 3.1 Hz, 0.5H), 7.97 (d, J = 3.1 Hz, 0.5H), 7.79 (d, J = 3.3 Hz, 1H), 7.48 (m, 1H), 7.43 (m, 1H), 7.08-7.22 (m, 1H), 6.18 (s, 0.5H), 6.16 (s, 0.5H), 4.21-4.71 (m, 3H), 4.01-4.20 (m, 4H), 3.82-3.99 (m, 3H), 3.43-3.78 (m, 3H), 2.38-2.56 (m, 1H), 2.32 (d, J = 11.5 Hz, 1H), 1.16 ppm (t, J = 7.1Hz, 1.5H), 1.15 (t, J = 7.1Hz, 1.5H).	LC/MS: calc'd 609, 611 (MH ⁺), exp 609, 611 (MH ⁺)
51	¹ H NMR (METHANOL-d ₄ , 400MHz): 8.02 (d, J = 3.3 Hz, 1H), 7.92 (d, J = 3.0 Hz, 1H), 7.55 (m, 1H), 7.30 (dd, J = 8.7, 2.6 Hz, 1H), 7.12 (td, J = 8.3, 2.6 Hz, 0.5H), 7.11 (dt, J = 8.3, 2.6 Hz, 0.5H), 6.21 (s, 0.5H), 6.20 (s, 0.5H), 5.75 (m, 0.5H), 5.61 (m, 0.5H), 4.92 (m, 1H), 4.71 (m, 1H), 4.29-4.54 (m, 2H), 4.18 (m, 3H), 3.89 (m, 1H), 3.65 (s, 1.5H), 3.64 (s, 1.5H), 2.58-2.97 (m, 2H).	LC/MS: calc'd 495 (MH ⁺), exp 495 (MH ⁺)

52	¹ H NMR (METHANOL-d ₄ , 400MHz): 7.97 (d, J = 3.3 Hz, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.45 (m, 1H), 7.42 (dd, J = 8.4, 2.6 Hz, 1H), 7.12 (td, J = 8.4, 2.5 Hz, 1H), 6.18 (s, 1H), 4.17 (m, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.97 (m, 2H), 3.90 (m, 2H), 3.69 (m, 1H), 3.45(m, 2H), 3.24 (m, 0.5H), 3.07 (m, 0.5H), 2.45 (m, 1H), 2.33 (m, 1H), 1.15 (t, J = 7.2 Hz, 3H).	LC/MS: calc'd 579, 581 (MH ⁺), exp 579, 581 (MH ⁺)
53	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (dd, J = 3.01, 1.76 Hz, 1 H) 7.76 (d, J = 3.01 Hz, 1 H) 7.35 - 7.46 (m, 2 H) 7.09 (d, J = 2.51 Hz, 1 H) 6.17 (s, 1 H) 4.70 (d, J = 17.57 Hz, 1 H) 4.54 (dd, J = 13.55, 2.51 Hz, 1 H) 4.11 - 4.36 (m, 5 H) 3.84 - 4.01 (m, 2 H) 3.73 - 3.84 (m, 2 H) 3.63 (s, 3 H) 3.40 - 3.52 (m, 1 H) 2.78 (t, J = 17.19 Hz, 2 H).	MS: calc'd (MH ⁺) 594, exp (MH ⁺) 594
54	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (d, J = 3.26 Hz, 1 H) 7.76 (d, J = 3.01 Hz, 1 H) 7.35 - 7.49 (m, 2 H) 7.09 (td, J = 8.41, 2.51 Hz, 1 H) 6.17 (s, 1 H) 4.68 (d, J = 17.57 Hz, 1 H) 4.11 - 4.25 (m, 3 H) 3.99 (d, J = 5.77 Hz, 2 H) 3.89 - 3.97 (m, 2 H) 3.63 (s, 3 H) 3.57 (br. s., 2 H) 2.78 (br. s., 1 H) 2.73 (br. s., 1 H).	MS: calc'd (MH ⁺) 579, exp (MH ⁺) 579
55	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.02 (d, J = 3.26 Hz, 1 H) 7.92 (d, J = 3.26 Hz, 1 H) 7.31 - 7.42 (m, 2 H) 7.25 (ddd, J = 9.10, 7.09, 2.38 Hz, 1 H) 6.22 - 6.30 (m, 1 H) 5.05 (d, J = 16.81 Hz, 1 H) 4.71 (d, J = 17.07 Hz, 1 H) 4.16 - 4.27 (m, 2 H) 3.85 (br. s., 2 H) 3.68 - 3.80 (m, 2 H) 3.60 - 3.68 (m, 3 H) 2.56 - 2.80 (m, 5 H) 1.90 (d, J = 6.53 Hz, 2 H).	LC/MS: calc'd 550 (MH ⁺), exp 550 (MH ⁺)
56	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.02 (d, J = 3.26 Hz, 1 H) 7.92 (d, J = 3.26 Hz, 1 H) 7.56 (dd, J = 8.78, 6.02 Hz, 1 H) 7.30 (dd, J = 8.66, 2.64 Hz, 1 H) 7.12 (td, J = 8.34, 2.64 Hz, 1 H) 6.16 - 6.25 (m, 1 H) 5.03 (d, J = 16.81 Hz, 1 H) 4.73 (d, J = 17.07 Hz, 1 H) 4.64 (dt, J = 11.98, 5.93 Hz, 1 H) 4.26 - 4.35 (m, 2 H) 4.12 - 4.24 (m, 2 H) 3.79 (br. s., 2 H) 3.67 (s, 3 H) 2.58 (br. s., 2 H) 2.20 - 2.38 (m, 2 H).	LC/MS: calc'd 586 (MH ⁺), exp 586 (MH ⁺)
57	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.02 (d, J = 3.26 Hz, 1 H) 7.93 (d, J = 3.26 Hz, 1 H) 7.56 (dd, J = 8.78, 6.02 Hz, 1 H)	LC/MS: calc'd 550 (MH ⁺), exp

	7.30 (dd, J = 8.78, 2.51 Hz, 1 H) 7.13 (td, J = 8.41, 2.76 Hz, 1 H) 6.21 (s, 1 H) 5.06 (d, J = 16.56 Hz, 1 H) 4.89 - 4.94 (m, 1 H) 4.76 (d, J = 16.56 Hz, 1 H) 4.09 - 4.35 (m, 4 H) 3.78 (br. s., 2 H) 3.67 (s, 3 H) 2.43 (br. s., 2 H) 2.10 - 2.28 (m, 2 H).	550 (MH ⁺)
58	¹ H NMR ((METHANOL-d ₄ , 400 MHz): 8.01 (d, J = 3.01 Hz, 1 H) 7.88 - 7.94 (m, 1 H) 7.52 - 7.65 (m, 1 H) 7.46 (d, J = 2.76 Hz, 1 H) 7.17 (td, J = 8.34, 2.64 Hz, 1 H) 6.20 (s, 1 H) 5.08 (d, J = 15.56 Hz, 1 H) 4.73 (dd, J = 16.06, 8.28 Hz, 1 H) 4.04 - 4.41 (m, 4 H) 3.61 - 3.86 (m, 5 H) 3.15 - 3.29 (m, 1 H) 2.21 - 2.55 (m, 4 H) 2.14 (t, J = 11.04 Hz, 2 H).	LC/MS: calc'd 594(MH ⁺), exp 594 (MH ⁺)
59	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 - 8.06 (m, 1 H) 7.92 (d, J = 3.26 Hz, 1 H) 7.32 - 7.45 (m, 2 H) 7.15 - 7.28 (m, 1 H) 6.26 (s, 1 H) 4.98 - 5.15 (m, 1 H) 4.63 - 4.77 (m, 1 H) 4.30 (br. s., 4 H) 3.59 - 3.83 (m, 5 H) 3.15 - 3.29 (m, 1 H) 2.62 - 2.77 (m, 1 H) 2.38 (d, J = 6.78 Hz, 3 H) 2.14 (br. s., 2 H).	LC/MS: calc'd 550 (MH ⁺), exp 550 (MH ⁺)
60	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.90 - 8.03 (m, 1 H) 7.76 (d, J = 3.26 Hz, 1 H) 7.41 (dd, J = 8.78, 6.02 Hz, 1 H) 7.23 (dd, J = 8.78, 2.51 Hz, 1 H) 7.04 (td, J = 8.41, 2.76 Hz, 1 H) 6.17 (s, 1 H) 4.53 (d, J = 17.57 Hz, 1 H) 4.01 - 4.23 (m, 3 H) 3.79 - 3.96 (m, 3 H) 3.63 (s, 3 H) 2.95 - 3.11 (m, 3 H) 2.82 (br. s., 1 H) 2.75 (br. s., 1 H) 2.51 - 2.65 (m, 2 H) 1.78 (dd, J = 13.55, 9.79 Hz, 2 H).	LC/MS: calc'd 585 (MH ⁺), exp 585 (MH ⁺)
61	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.99 (d, J = 3.01 Hz, 1 H) 7.76 (d, J = 3.26 Hz, 1 H) 7.41 (dd, J = 8.66, 6.15 Hz, 1 H) 7.24 (dd, J = 8.78, 2.76 Hz, 1 H) 7.04 (td, J = 8.41, 2.76 Hz, 1 H) 6.17 (s, 1 H) 4.55 (d, J = 17.82 Hz, 1 H) 4.45 (t, J = 6.65 Hz, 1 H) 4.02 - 4.19 (m, 3 H) 3.76 - 3.92 (m, 2 H) 3.63 (s, 3 H) 2.80 (br. s., 1 H) 2.73 (br. s., 1 H) 2.43 - 2.58 (m, 2 H) 1.93 - 2.05 (m, 3 H) 1.51 - 1.66 (m, 2 H).	LC/MS: calc'd 549 (MH ⁺), exp 549 (MH ⁺)
62	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (d, J = 3.26 Hz, 1 H) 7.75 (d, J = 3.01 Hz, 1 H) 7.40 (dd, J = 8.66, 6.15 Hz, 1 H) 7.23 (dd, J = 8.78, 2.51 Hz, 1 H) 7.04 (d, J = 2.51 Hz, 1 H) 6.17 (s, 1 H) 4.53 (d, J = 17.82 Hz, 1 H) 4.18 - 4.32 (m, 1 H) 4.01 -	LC/MS: calc'd 550 (MH ⁺), exp 550 (MH ⁺)

	4.18 (m, 3 H) 3.77 - 3.91 (m, 2 H) 3.63 (s, 3 H) 2.70 - 2.79 (m, 2 H) 2.53 (dq, J = 14.40, 7.08 Hz, 2 H) 1.59 (dd, J = 14.43, 9.91 Hz, 2 H).	
63	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.99 (d, J = 3.01 Hz, 1 H) 7.78 (d, J = 2.76 Hz, 1 H) 7.39 - 7.47 (m, 1 H) 7.25 (dd, J = 8.78, 2.51 Hz, 1 H) 7.05 (td, J = 8.34, 2.64 Hz, 1 H) 6.18 (s, 1 H) 4.58 (d, J = 17.82 Hz, 1 H) 4.16 (d, J = 10.04 Hz, 3 H) 3.77 - 3.98 (m, 3 H) 3.63 (s, 3 H) 2.83 (br. s., 2 H) 2.55 (br. s., 2 H) 1.95 (br. s., 2 H).	LC/MS: calc'd 586 (MH ⁺), exp 586 (MH ⁺)
64	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.92 - 8.03 (m, 1 H) 7.71 - 7.84 (m, 1 H) 7.36 - 7.52 (m, 2 H) 7.11 (td, J = 8.41, 2.51 Hz, 1 H) 6.16 (s, 1 H) 4.32 (d, J = 16.81 Hz, 1 H) 4.12 (d, J = 17.32 Hz, 1 H) 3.84 - 4.04 (m, 3 H) 3.70 (d, J = 10.79 Hz, 1 H) 3.62 (s, 3 H) 3.44 (d, J = 9.29 Hz, 1 H) 3.27 (br. s., 1 H) 2.84 - 2.98 (m, 1 H) 2.64 - 2.81 (m, 2 H) 2.56 (td, J = 12.05, 7.28 Hz, 1 H) 1.70 (dd, J = 12.92, 5.14 Hz, 1 H).	LC/MS: calc'd 579 (MH ⁺), exp 579 (MH ⁺)
65	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.02 (d, J = 3.01 Hz, 1 H) 7.86 - 7.94 (m, 1 H) 7.30 - 7.47 (m, 2 H) 7.25 (ddd, J = 9.16, 7.40, 2.01 Hz, 1 H) 6.28 (s, 1 H) 5.04 (d, J = 17.07 Hz, 1 H) 4.71 (d, J = 16.81 Hz, 1 H) 4.04 - 4.28 (m, 4 H) 3.86 (br. s., 2 H) 3.63 - 3.78 (m, 2 H) 2.69 (d, J = 4.77 Hz, 5 H) 1.90 (d, J = 6.53 Hz, 2 H) 1.14 (t, J = 7.15 Hz, 3 H).	LC/MS: calc'd 564 (MH ⁺), exp 564 (MH ⁺)
66	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.01 Hz, 1 H) 7.77 (d, J = 3.01 Hz, 1 H) 7.21 - 7.34 (m, 2 H) 7.15 (td, J = 8.47, 1.88 Hz, 1 H) 6.24 (s, 1 H) 4.54 (d, J = 17.57 Hz, 1 H) 4.07 (dd, J = 7.15, 0.88 Hz, 5 H) 3.84 - 3.96 (m, 2 H) 3.07 - 3.21 (m, 1 H) 2.65 - 2.85 (m, 2 H) 2.23 (d, J = 7.03 Hz, 2 H) 1.70 - 1.94 (m, 4 H) 1.16 (t, J = 7.15 Hz, 3 H).	LC/MS: calc'd 564 (MH ⁺), exp 564 (MH ⁺)
67	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.88 - 8.04 (m, 1 H) 7.66 - 7.81 (m, 1 H) 7.35 - 7.48 (m, 2 H) 7.10 (td, J = 8.41, 2.51 Hz, 1 H) 6.11 - 6.22 (m, 1 H) 4.58 (d, J = 17.57 Hz, 1 H) 4.01 - 4.27 (m, 5 H) 3.92 (t, J = 11.17 Hz, 2 H) 3.15 (tt, J = 12.30, 6.02 Hz, 1 H) 2.76 - 2.94 (m, 2 H) 2.17 - 2.31 (m, 2 H) 1.73 -	LC/MS: calc'd 608 (MH ⁺), exp 608 (MH ⁺)

	1.99 (m, 4 H) 1.09 - 1.24 (m, 3 H).	
68	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.92 - 8.02 (m, 1 H) 7.77 (d, J = 3.26 Hz, 1 H) 7.29 - 7.39 (m, 1 H) 7.24 (d, J = 7.78 Hz, 1 H) 7.13 (td, J = 8.28, 1.25 Hz, 1 H) 6.25 (s, 1 H) 4.60 (d, J = 17.07 Hz, 1 H) 4.10 - 4.27 (m, 3 H) 4.01 - 4.10 (m, 2 H) 3.85 - 3.98 (m, 2 H) 3.15 (tt, J = 12.23, 6.21 Hz, 1 H) 2.74 - 2.98 (m, 2 H) 2.25 (d, J = 7.28 Hz, 2 H) 1.77 - 2.00 (m, 4 H) 1.15 (t, J = 7.15 Hz, 3 H).	LC/MS: calc'd 608 (MH ⁺), exp 608 (MH ⁺)
69	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.93 - 8.01 (m, 1 H) 7.77 (d, J = 3.01 Hz, 1 H) 7.13 - 7.28 (m, 2 H) 6.18 (s, 1 H) 4.54 (d, J = 17.82 Hz, 1 H) 4.01 - 4.19 (m, 5 H) 3.91 (t, J = 11.54 Hz, 2 H) 3.04 - 3.20 (m, 1 H) 2.69 - 2.88 (m, 2 H) 2.23 (d, J = 7.03 Hz, 2 H) 1.73 - 1.96 (m, 4 H) 1.17 (t, J = 7.03 Hz, 3 H).	LC/MS: calc'd 582 (MH ⁺), exp 582 (MH ⁺)
70	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 - 8.07 (m, 1 H) 7.92 (d, J = 3.01 Hz, 1 H) 7.54 - 7.65 (m, 1 H) 7.48 (dd, J = 8.41, 2.64 Hz, 1 H) 7.18 (td, J = 8.34, 2.64 Hz, 1 H) 6.22 (s, 1 H) 5.00 - 5.17 (m, 2 H) 4.78 (d, J = 16.81 Hz, 1 H) 4.26 - 4.38 (m, 2 H) 4.03 - 4.24 (m, 4 H) 3.81 (br. s., 2 H) 2.41 (br. s., 2 H) 2.18 - 2.32 (m, 2 H) 1.93 - 2.09 (m, 3 H) 1.16 (t, J = 7.03 Hz, 3 H).	LC/MS: calc'd 606 (MH ⁺), exp 606 (MH ⁺)
71	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.02 (d, J = 3.01 Hz, 1 H) 7.93 (d, J = 3.01 Hz, 1 H) 7.57 (dd, J = 8.78, 6.02 Hz, 1 H) 7.48 (dd, J = 8.41, 2.64 Hz, 1 H) 7.18 (td, J = 8.34, 2.64 Hz, 1 H) 6.22 (s, 1 H) 5.03 (d, J = 16.81 Hz, 1 H) 4.73 (d, J = 16.56 Hz, 1 H) 4.51 (t, J = 7.03 Hz, 1 H) 4.25 - 4.37 (m, 2 H) 4.04 - 4.22 (m, 4 H) 3.75 (d, J = 4.27 Hz, 2 H) 2.73 - 2.88 (m, 2 H) 2.03 - 2.16 (m, 2 H) 1.95 - 2.03 (m, 3 H) 1.16 (t, J = 7.15 Hz, 3 H).	LC/MS: calc'd 606 (MH ⁺), exp 606 (MH ⁺)
72	¹ H NMR (DMSO-d ₆ , 400 MHz): 12.04 (br. s., 1 H) 9.98 (s, 1 H) 8.01 - 8.09 (m, 1 H) 7.95 (d, J = 3.01 Hz, 1 H) 7.44 (dd, J = 7.53, 1.76 Hz, 1 H) 7.38 (dd, J = 7.53, 2.01 Hz, 1 H) 7.21 - 7.32 (m, 2 H) 6.09 (s, 1 H) 4.33 (d, J = 17.82 Hz, 1 H) 3.85 - 4.09 (m, 5 H) 3.71 - 3.83 (m, 2 H) 2.94 (dt, J = 12.36, 6.24 Hz, 1 H)	LC/MS: calc'd 546 (MH ⁺), exp 546 (MH ⁺)

	2.75 (br. s., 1 H) 2.64 (br. s., 1 H) 2.09 (d, J = 7.03 Hz, 2 H) 1.73 (td, J = 12.05, 5.02 Hz, 2 H) 1.60 (d, J = 13.05 Hz, 2 H) 1.08 (t, J = 7.03 Hz, 3 H).	
73	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.01 Hz, 1 H) 7.77 (d, J = 3.01 Hz, 1 H) 7.14 - 7.29 (m, 2 H) 6.17 (s, 1 H) 4.53 (d, J = 17.32 Hz, 1 H) 4.01 - 4.21 (m, 3 H) 3.90 (t, J = 11.67 Hz, 2 H) 3.63 (s, 3 H) 3.08 - 3.22 (m, 1 H) 2.64 - 2.84 (m, 2 H) 2.24 (d, J = 6.78 Hz, 2 H) 1.70 - 1.98 (m, 4 H).	LC/MS: calc'd 568 (MH ⁺), exp 568 (MH ⁺)
74	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.01 Hz, 1 H) 7.76 (d, J = 3.01 Hz, 1 H) 7.33 (td, J = 7.97, 5.40 Hz, 1 H) 7.21 (d, J = 7.78 Hz, 1 H) 7.11 (td, J = 8.28, 1.51 Hz, 1 H) 6.23 (s, 1 H) 4.54 (d, J = 18.07 Hz, 1 H) 4.01 - 4.20 (m, 3 H) 3.90 (t, J = 11.92 Hz, 2 H) 3.62 (s, 3 H) 3.13 (dd, J = 12.92, 5.90 Hz, 1 H) 2.65 - 2.85 (m, 2 H) 2.24 (d, J = 7.03 Hz, 2 H) 1.86 (d, J = 8.53 Hz, 4 H).	LC/MS: calc'd 594 (MH ⁺), exp 594 (MH ⁺)
75	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.00 (d, J = 3.01 Hz, 1 H) 7.80 (d, J = 3.01 Hz, 1 H) 7.03 - 7.26 (m, 3 H) 6.07 (s, 1 H) 4.51 (br. s., 1 H) 4.04 - 4.24 (m, 5 H) 3.94 (d, J = 11.80 Hz, 2 H) 3.05 - 3.19 (m, 1 H) 2.82 (br. s., 2 H) 2.24 (d, J = 7.03 Hz, 2 H) 1.84 (br. s., 4 H) 1.21 (t, J = 7.15 Hz, 3 H).	LC/MS: calc'd 547 (MH ⁺), exp 547 (MH ⁺)
76	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (d, J = 3.26 Hz, 1 H) 7.76 (d, J = 3.01 Hz, 1 H) 7.61 (dd, J = 8.03, 1.25 Hz, 1 H) 7.35 - 7.43 (m, 1 H) 7.31 (td, J = 7.47, 1.13 Hz, 1 H) 7.15 (td, J = 7.65, 1.76 Hz, 1 H) 6.19 (s, 1 H) 4.55 (d, J = 18.07 Hz, 1 H) 4.02 - 4.25 (m, 3 H) 3.84 - 3.96 (m, 2 H) 3.63 (s, 3 H) 3.08 - 3.19 (m, 1 H) 2.66 - 2.87 (m, 2 H) 2.24 (d, J = 7.03 Hz, 2 H) 1.73 - 1.99 (m, 4 H).	LC/MS: calc'd 576 (MH ⁺), exp 576 (MH ⁺)
77	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.26 Hz, 1 H) 7.75 (d, J = 3.26 Hz, 1 H) 7.61 (dd, J = 8.03, 1.25 Hz, 1 H) 7.35 - 7.45 (m, 1 H) 7.27 - 7.34 (m, 1 H) 7.16 (td, J = 7.65, 1.76 Hz, 1 H) 6.16 - 6.22 (m, 1 H) 4.54 (d, J = 17.57 Hz, 1 H) 3.99 - 4.21 (m, 5 H) 3.90 (t, J = 12.17 Hz, 2 H) 3.13 (dd, J = 12.05, 6.02 Hz, 1 H) 2.62 - 2.84 (m, 2 H) 2.22 (d, J = 7.03 Hz, 2 H)	LC/MS: calc'd 590 (MH ⁺), exp 590 (MH ⁺)

	1.74 - 1.95 (m, 4 H) 1.16 (t, J = 7.15 Hz, 3 H) ¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.26 Hz, 1 H) 7.75 (d, J = 3.26 Hz, 1 H) 7.61 (dd, J = 8.03, 1.25 Hz, 1 H) 7.35 - 7.45 (m, 1 H) 7.27 - 7.34 (m, 1 H) 7.16 (td, J = 7.65, 1.76 Hz, 1 H) 6.16 - 6.22 (m, 1 H) 4.54 (d, J = 17.57 Hz, 1 H) 3.99 - 4.21 (m, 5 H) 3.90 (t, J = 12.17 Hz, 2 H) 3.13 (dd, J = 12.05, 6.02 Hz, 1 H) 2.62 - 2.84 (m, 2 H) 2.22 (d, J = 7.03 Hz, 2 H) 1.74 - 1.95 (m, 4 H) 1.16 (t, J = 7.15 Hz, 3 H).	
78	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (d, J = 3.26 Hz, 1 H) 7.75 (d, J = 3.26 Hz, 1 H) 6.95 - 7.12 (m, 2 H) 5.93 (s, 1 H) 4.57 (d, J = 17.57 Hz, 1 H) 4.03 - 4.22 (m, 5 H) 3.91 (t, J = 12.17 Hz, 2 H) 3.07 - 3.21 (m, 1 H) 2.68 - 2.88 (m, 2 H) 2.23 (d, J = 7.03 Hz, 2 H) 1.72 - 1.98 (m, 4 H) 1.19 (t, J = 7.15 Hz, 3 H).	LC/MS: calc'd 561 (MH ⁺), exp 561 (MH ⁺)
79	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.00 (d, J = 3.01 Hz, 1 H) 7.83 (d, J = 3.26 Hz, 1 H) 7.47 (dd, J = 8.66, 6.15 Hz, 1 H) 7.22 - 7.31 (m, 1 H) 7.07 (td, J = 8.41, 2.76 Hz, 1 H) 6.20 (s, 1 H) 4.77 (d, J = 16.81 Hz, 1 H) 4.65 (br. s., 1 H) 4.33 (d, J = 17.57 Hz, 1 H) 4.18 (d, J = 11.80 Hz, 2 H) 4.00 (d, J = 17.07 Hz, 2 H) 3.84 (br. s., 2 H) 3.64 (s, 3 H) 3.48 (d, J = 18.82 Hz, 1 H) 3.02 (br. s., 2 H) 1.36 - 1.58 (m, 6 H).	LC/MS: calc'd 607 (MH ⁺), exp 607 (MH ⁺)
80	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.91 - 8.04 (m, 1 H) 7.76 (d, J = 3.01 Hz, 1 H) 7.17 - 7.31 (m, 2 H) 6.19 (s, 1 H) 4.55 (d, J = 17.82 Hz, 1 H) 3.99 - 4.22 (m, 5 H) 3.91 (t, J = 11.67 Hz, 2 H) 3.13 (td, J = 11.92, 6.02 Hz, 1 H) 2.67 - 2.87 (m, 2 H) 2.23 (d, J = 7.03 Hz, 2 H) 1.71 - 1.96 (m, 4 H) 1.17 (t, J = 7.15 Hz, 3 H).	LC/MS: calc'd 626 (MH ⁺), exp 626 (MH ⁺)
81	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.95 - 8.02 (m, 1 H) 7.80 - 7.88 (m, 1 H) 7.50 - 7.60 (m, 1 H) 7.21 - 7.30 (m, 1 H) 7.01 - 7.12 (m, 1 H) 6.13 - 6.22 (m, 1 H) 4.67 - 4.79 (m, 1 H) 4.36 - 4.49 (m, 1 H) 4.07 - 4.22 (m, 2 H) 3.94 - 4.04 (m, 1 H) 3.70 - 3.85 (m, 2 H) 3.62 (s, 3 H) 2.26 - 2.50 (m, 3 H) 2.14 - 2.26 (m, 1 H).	LC/MS: calc'd 521 (MH ⁺), exp 521 (MH ⁺)
82	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, J = 3.14 Hz, 1	LC/MS: calc'd

	H) 7.84 (s, 1 H) 7.49 - 7.57 (m, 1 H) 7.21 - 7.30 (m, 1 H) 7.04 - 7.15 (m, 1 H) 6.19 (s, 1 H) 4.80 - 4.89 (m, 1 H) 4.28 - 4.39 (m, 1 H) 4.08 - 4.20 (m, 2 H) 3.91 - 4.02 (m, 1 H) 3.80 - 3.90 (m, 1 H) 3.70 - 3.79 (m, 1 H) 3.62 (s, 3 H) 2.31 - 2.50 (m, 3 H) 2.15 - 2.27 (m, 1 H).	521 (MH ⁺), exp 521 (MH ⁺)
83	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.96 - 8.02 (m, 1 H) 7.78 - 7.86 (m, 1 H) 7.30 - 7.44 (m, 2 H) 7.16 - 7.23 (m, 1 H) 6.25 (s, 1 H) 4.17 - 4.46 (m, 2 H) 4.00 - 4.16 (m, 4 H) 3.88 - 3.96 (m, 1 H) 3.66 - 3.81 (m, 2 H) 2.27 - 2.48 (m, 3 H) 2.13 - 2.22 (m, 1 H) 1.13 (td, J = 7.12, 1.94 Hz, 3 H).	LC/MS: calc'd 535 (MH ⁺), exp 535(MH ⁺)
84	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.97 (d, J = 3.14 Hz, 1 H) 7.79 (m, 1 H) 7.22 (m, 1 H) 7.00 - 7.12 (m, 1 H) 5.92 (s, 1 H) 4.75-4.86 (m, 1 H) 4.09 (m, 3 H) 3.92 (m, 2 H) 3.68 - 3.76 (m, 1 H) 3.62 (s, 3 H) 2.54 (d, J = 2.26 Hz, 3 H) 2.35 (m, 3 H) 2.04 - 2.16 (m, 1 H).	LC/MS: calc'd 519 (MH ⁺), exp 519(MH ⁺)
85	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.96 (d, J = 3.14 Hz, 1 H) 7.72 - 7.84 (m, 1 H) 7.13 - 7.27 (m, 1 H) 7.05 (d, J = 9.29 Hz, 1 H) 5.93 (s, 1 H) 4.65 - 4.78 (m, 1 H) 4.15 - 4.26 (m, 1 H) 4.01 - 4.14 (m, 3 H) 3.86 - 3.97 (m, 1 H) 3.66 - 3.75 (m, 1 H) 3.63 (s, 3 H) 2.54 (d, J = 2.13 Hz, 3 H) 2.25 - 2.44 (m, 3 H) 2.09 - 2.22 (m, 1 H).	LC/MS: calc'd 519 (MH ⁺), exp 519(MH ⁺)
86	¹ H NMR (400MHz, METHANOL-d ₄) 8.06 - 7.93 (m, 1H), 7.79 - 7.72 (m, 1H), 7.47 - 7.37 (m, 1H), 7.32 - 7.18 (m, 1H), 7.13 - 6.98 (m, 1H), 6.22 - 6.12 (m, 1H), 4.30 - 4.20 (m, 2H), 3.62 (s, 2H), 3.53 - 3.44 (m, 1H), 3.31 - 3.24 (m, 1H), 2.88 - 2.65 (m, 2H), 2.50 - 2.21 (m, 4H), 2.05 - 1.93 (m, 1H), 1.84 - 1.58 (m, 3H).	LC/MS: calc'd 569 (MH ⁺), exp 569(MH ⁺)
87	¹ H NMR (400MHz, METHANOL-d ₄) 8.04 - 7.88 (m, 1H), 7.83 - 7.69 (m, 1H), 7.29 - 7.20 (m, 1H), 7.11 - 7.00 (m, 1H), 6.18 (s, 1H), 4.59 - 4.46 (m, 1H), 4.03 - 3.92 (m, 1H), 3.61 (s, 3H), 3.38 (br. s., 2H), 2.85 - 2.60 (m, 2H), 2.35 (s, 4H), 2.11 - 2.01 (m, 1H), 1.90 - 1.62 (m, 3H).	LC/MS: calc'd 569 (MH ⁺), exp 569(MH ⁺)
88	¹ H NMR (400MHz, METHANOL-d ₄) 7.97 (d, J = 3.0 Hz, 1H),	LC/MS: calc'd

	7.76 (d, J = 3.0 Hz, 1H), 7.39 - 7.21 (m, 2H), 7.19 - 7.10 (m, 1H), 6.23 (s, 1H), 4.26 (s, 2H), 3.61 (s, 3H), 3.50 (br. s., 1H), 2.91 - 2.61 (m, 2H), 2.51 - 2.19 (m, 4H), 1.98 (d, J = 12.0 Hz, 1H), 1.87 - 1.60 (m, 3H).	569 (MH ⁺), exp 569(MH ⁺)
89	¹ H NMR (400MHz, METHANOL-d ₄) 8.02 - 7.90 (m, 1H), 7.79 - 7.71 (m, 1H), 7.37 - 7.21 (m, 2H), 7.19 - 7.10 (m, 1H), 6.23 (s, 1H), 4.56 - 4.44 (m, 1H), 4.06 - 3.89 (m, 2H), 3.61 (s, 3H), 3.39 (br. s., 1H), 2.86 - 2.61 (m, 2H), 2.50 - 2.19 (m, 4H), 2.04 (d, J = 14.1 Hz, 1H), 1.90 - 1.63 (m, 3H).	LC/MS: calc'd 569 (MH ⁺), exp 569(MH ⁺)
90	¹ H NMR (400MHz, METHANOL-d ₄) 8.04 - 7.94 (m, 1H), 7.78 - 7.70 (m, 1H), 7.45 - 7.36 (m, 2H), 7.30 - 7.19 (m, 2H), 6.20 (s, 1H), 4.24 (s, 2H), 3.60 (s, 3H), 3.53 - 3.43 (m, 1H), 3.30 - 3.25 (m, 1H), 2.86 - 2.66 (m, 1H), 2.50 - 2.22 (m, 4H), 2.03 - 1.92 (m, 1H), 1.86 - 1.61 (m, 3H).	LC/MS: calc'd 551 (MH ⁺), exp 551(MH ⁺)
91	¹ H NMR (400MHz, METHANOL-d ₄) 7.96 (d, J = 3.3 Hz, 1H), 7.74 (d, J = 3.3 Hz, 1H), 7.48 - 7.33 (m, 2H), 7.25 (ddd, J = 1.6, 7.3, 9.1 Hz, 2H), 6.22 (s, 1H), 4.46 (d, J = 1.8 Hz, 1H), 3.96 (d, J = 17.8 Hz, 1H), 3.60 (s, 3H), 3.42 - 3.38 (m, 1H), 3.37 (br. s., 2H), 2.82 - 2.63 (m, 1H), 2.48 - 2.21 (m, 4H), 2.09 - 1.98 (m, 1H), 1.89 - 1.59 (m, 3H).	LC/MS: calc'd 551 (MH ⁺), exp 551(MH ⁺)
92	¹ H NMR (400MHz, METHANOL-d ₄) 8.01 - 7.90 (m, 1H), 7.78 - 7.70 (m, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.45 - 7.37 (m, 1H), 7.32 (s, 1H), 7.21 - 7.07 (m, 1H), 6.19 (s, 1H), 4.25 (s, 2H), 4.04 (q, J = 7.0 Hz, 2H), 3.55 - 3.47 (m, 1H), 3.30 (br. s., 1H), 2.71 (d, J = 5.0 Hz, 1H), 2.48 - 2.22 (m, 4H), 1.96 (br. s., 1H), 1.86 - 1.61 (m, 3H), 1.15 (t, J = 7.0 Hz, 3H).	LC/MS: calc'd 609 (MH ⁺), exp 609 (MH ⁺)
93	¹ H NMR (400MHz, METHANOL-d ₄) 7.96 (d, J = 3.3 Hz, 1H), 7.73 (d, J = 3.0 Hz, 1H), 7.60 (dd, J = 1.1, 7.9 Hz, 1H), 7.41 (dd, J = 1.8, 7.8 Hz, 1H), 7.32 (dt, J = 1.0, 7.5 Hz, 1H), 7.15 (dt, J = 1.8, 7.7 Hz, 1H), 6.20 (s, 1H), 4.49 (dd, J = 1.6, 17.7 Hz, 1H), 4.11 - 3.90 (m, 3H), 3.39 (d, J = 8.3 Hz, 2H), 2.71 (s, 1H), 2.48 - 2.17 (m, 4H), 2.04 (d, J = 13.6 Hz, 1H), 1.89 - 1.73 (m, 2H), 1.66 (t, J = 12.7 Hz, 1H), 1.15 (t, J = 7.2 Hz, 3H).	LC/MS: calc'd 609 (MH ⁺), exp 609 (MH ⁺)

94	¹ H NMR (400MHz, METHANOL-d4) 8.02 - 7.93 (m, 1H), 7.79 - 7.69 (m, 1H), 7.41 - 7.28 (m, 1H), 7.27 - 7.18 (m, 1H), 7.15 - 7.03 (m, 1H), 6.22 (s, 1H), 4.25 (s, 2H), 3.60 (s, 3H), 3.51 - 3.42 (m, 1H), 3.31 - 3.22 (m, 1H), 2.85 - 2.66 (m, 1H), 2.49 - 2.18 (m, 4H), 2.05 - 1.91 (m, 1H), 1.85 - 1.61 (m, 3H).	LC/MS: calc'd 613 (MH ⁺), exp 613 (MH ⁺)
95	¹ H NMR (400MHz, METHANOL-d4) 8.02 - 7.90 (m, 1H), 7.81 - 7.64 (m, 1H), 7.39 - 7.27 (m, 1H), 7.26 - 7.18 (m, 1H), 7.15 - 7.04 (m, 1H), 6.28 - 6.16 (m, 1H), 4.57 - 4.41 (m, 1H), 4.04 - 3.90 (m, 1H), 3.60 (s, 3H), 3.44 - 3.34 (m, 2H), 2.79 - 2.63 (m, 1H), 2.28 (s, 4H), 2.08 - 1.96 (m, 1H), 1.87 - 1.58 (m, 3H).	LC/MS: calc'd 613 (MH ⁺), exp 613 (MH ⁺)
96	¹ H NMR (400MHz, METHANOL-d4) 8.07 - 7.98 (m, 1H), 7.83 - 7.74 (m, 1H), 7.52 - 7.37 (m, 1H), 7.26 - 7.13 (m, 2H), 5.74 (s, 1H), 4.33 - 4.06 (m, 2H), 3.70 (s, 3H), 3.46 - 3.37 (m, 1H), 3.29 - 3.20 (m, 1H), 2.82 - 2.62 (m, 1H), 2.46 - 2.15 (m, 4H), 2.02 - 1.89 (m, 1H), 1.85 - 1.57 (m, 3H).	LC/MS: calc'd 569 (MH ⁺), exp 569 (MH ⁺)
97	¹ H NMR (400MHz, METHANOL-d4) 8.13 - 7.94 (m, 1H), 7.85 - 7.74 (m, 1H), 7.48 - 7.35 (m, 1H), 7.30 - 7.08 (m, 2H), 5.79 - 5.67 (m, 1H), 4.57 - 4.41 (m, 1H), 3.99 - 3.84 (m, 1H), 3.70 (s, 3H), 3.39 - 3.34 (m, 1H), 3.32 - 3.26 (m, 1H), 2.80 - 2.60 (m, 1H), 2.48 - 2.16 (m, 4H), 2.07 - 1.94 (m, 1H), 1.88 - 1.54 (m, 3H).	LC/MS: calc'd 569 (MH ⁺), exp 569 (MH ⁺)
98	¹ H NMR (400MHz, METHANOL-d4) 7.98 (d, J = 3.3 Hz, 1H), 7.75 (d, J = 3.3 Hz, 1H), 7.36 - 7.21 (m, 2H), 7.19 - 7.10 (m, 1H), 6.27 - 6.16 (m, 1H), 4.24 (d, J = 4.3 Hz, 2H), 4.12 - 3.99 (m, 2H), 3.47 (d, J = 6.5 Hz, 1H), 3.30 (d, J = 12.8 Hz, 1H), 2.84 - 2.62 (m, 1H), 2.48 - 2.16 (m, 4H), 2.03 - 1.91 (m, 1H), 1.86 - 1.60 (m, 3H), 1.15 (t, J = 7.0 Hz, 3H).	LC/MS: calc'd 583 (MH ⁺), exp 583 (MH ⁺)
99	¹ H NMR (400MHz, METHANOL-d4) 8.06 - 7.89 (m, 1H), 7.80 - 7.67 (m, 1H), 7.35 - 7.20 (m, 2H), 7.19 - 7.05 (m, 1H), 6.29 - 6.13 (m, 1H), 4.56 - 4.38 (m, 1H), 4.13 - 4.00 (m, 2H), 4.00 - 3.89 (m, 1H), 3.34 (s, 2H), 2.79 - 2.61 (m, 1H), 2.51 - 2.17 (m, 4H), 2.11 - 1.98 (m, 1H), 1.88 - 1.57 (m, 3H), 1.15 (t, J = 7.2 Hz, 3H).	LC/MS: calc'd 583 (MH ⁺), exp 583 (MH ⁺)

100	¹ H NMR (400MHz, METHANOL-d4) 7.97 - 7.89 (m, 1H), 7.81 - 7.75 (m, 1H), 7.27 - 7.19 (m, 2H), 7.16 - 7.05 (m, 1H), 6.19 - 6.12 (m, 1H), 4.98 - 4.91 (m, 1H), 4.89 - 4.83 (m, 1H), 4.50 (s, 1H), 4.14 - 4.02 (m, 2H), 3.93 - 3.85 (m, 1H), 3.70 - 3.62 (m, 1H), 3.60 - 3.56 (m, 1H), 3.44 - 3.38 (m, 1H), 2.85 - 2.75 (m, 2H), 2.75 - 2.62 (m, 2H), 2.60 - 2.49 (m, 1H), 1.71 - 1.58 (m, 1H).	LC/MS: calc'd 567 (MH ⁺), exp 567 (MH ⁺)
101	¹ H NMR (400MHz, METHANOL-d4) 7.92 (s, 1H), 7.79 (d, J = 3.0 Hz, 1H), 7.23 (s, 2H), 7.16 - 7.03 (m, 1H), 6.16 (s, 1H), 4.93 - 4.85 (m, 1H), 4.64 - 4.52 (m, 1H), 4.15 - 3.99 (m, 2H), 3.95 - 3.83 (m, 1H), 3.66 - 3.59 (m, 1H), 3.54 (s, 3H), 3.42 - 3.32 (m, 1H), 2.87 - 2.69 (m, 2H), 2.69 - 2.59 (m, 1H), 2.59 - 2.45 (m, 1H), 1.73 - 1.56 (m, 1H), 1.35 - 1.05 (m, 1H).	LC/MS: calc'd 567 (MH ⁺), exp 567 (MH ⁺)
102	¹ H NMR (400MHz, METHANOL-d4) 8.07 - 7.96 (m, 1H), 7.79 - 7.66 (m, 1H), 7.48 - 7.34 (m, 2H), 7.32 - 7.14 (m, 2H), 6.30 - 6.14 (m, 1H), 4.78 - 4.70 (m, 1H), 4.64 - 4.54 (m, 1H), 4.40 - 4.24 (m, 1H), 4.15 - 3.81 (m, 4H), 3.81 - 3.70 (m, 1H), 3.51 - 3.42 (m, 1H), 3.12 - 2.98 (m, 1H), 2.96 - 2.73 (m, 3H), 2.64 - 2.50 (m, 1H), 2.49 - 2.39 (m, 1H), 1.52 - 1.37 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H).	LC/MS: calc'd 563(MH ⁺), exp 563(MH ⁺)
103	¹ H NMR (400MHz, METHANOL-d4) 8.02 - 7.90 (m, 1H), 7.73 (d, J = 3.3 Hz, 1H), 7.42 (ddd, J = 1.6, 5.1, 7.3 Hz, 2H), 7.33 - 7.14 (m, 2H), 6.22 (s, 1H), 4.75 - 4.67 (m, 1H), 4.65 (s, 1H), 4.59 (s, 2H), 4.57 (s, 1H), 4.23 (d, J = 17.6 Hz, 1H), 4.13 - 3.93 (m, 4H), 3.78 (d, J = 11.3 Hz, 1H), 3.49 (d, J = 11.0 Hz, 1H), 3.11 - 2.96 (m, 1H), 2.91 (d, J = 8.8 Hz, 1H), 2.87 - 2.73 (m, 2H), 2.62 - 2.39 (m, 2H), 1.49 - 1.35 (m, 1H), 1.16 (t, J = 7.2 Hz, 3H).	LC/MS: calc'd 563(MH ⁺), exp 563(MH ⁺)
104	¹ H NMR (CD ₃ OD, 400 MHz): ppm 8.51 (s, 0.5H), 8.45 (s, 0.5H), 7.99 (t, J = 3.2 Hz, 1H), 7.78 (m, 1H), 7.42 (m, 1H), 7.25 (dd, J = 8.8, 2.4 Hz, 1H), 7.05 (m, 1H), 6.17 (s, 0.5H), 6.16 (s, 0.5H), 4.15 (m, 3H), 3.95 (m, 3H), 3.70 (m, 1H), 3.54 (s, 1.5H), 3.52 (s, 1.5H), 3.32 (m, 1H), 3.27 (m, 1H), 2.90 (m, 1H).	LC/MS: calc'd 530 (MH ⁺), exp 530 (MH ⁺)

105	¹ H NMR (400MHz, METHANOL-d ₄) 8.35 (s, 0.5H), 8.29 (s, 0.5H), 8.00 (t, J = 3.2 Hz, 1H), 7.78 (dd, J = 2.4, 3.0 Hz, 1H), 7.45-7.41 (m, 1H), 7.24 (dd, J = 2.4, 8.7 Hz, 1H), 7.09-7.02 (m, 1H), 6.17 (s, 0.5H), 6.16 (s, 0.5H), 4.20 - 3.75 (m, 6H), 3.71 - 3.58 (m, 1H), 3.54 (s, 1.5H), 3.52 (s, 1.5H), 3.32 - 3.18 (m, 2H), 2.93 - 2.76 (m, 1H).	LC/MS: calc'd 530 (MH ⁺), exp 530 (MH ⁺)
106	¹ H NMR (400MHz, METHANOL-d ₄) 8.50 (s, 0.6H), 8.44 (s, 0.4H), 8.06 - 7.91 (m, 1H), 7.78 (dd, J = 1.8, 3.0 Hz, 1H), 7.52 - 7.35 (m, 1H), 7.24 (dd, J = 2.5, 8.8 Hz, 1H), 7.13 - 6.97 (m, 1H), 6.18 (br, 1H), 5.86 - 5.59 (m, 1H), 4.51 - 4.20 (m, 1H), 4.16 - 3.85 (m, 5H), 3.75 - 3.41 (m, 5H).	LC/MS: calc'd 548 (MH ⁺), exp 548 (MH ⁺)
107	¹ H NMR (400MHz, METHANOL-d ₄) : 8.15 (dd, J = 1.5, 3.0 Hz, 1H), 8.03 (dd, J = 3.0, 6.8 Hz, 1H), 7.63 (d, J = 18.6 Hz, 1H), 7.55 - 7.52 (m, 1H), 7.35 - 7.26 (m, 1H), 7.20 - 7.07 (m, 1H), 6.26 (s, 0.5H), 6.25 (s, 0.5H), 4.46 (dd, J = 2.1, 17.4 Hz, 1H), 4.35 - 4.00 (m, 4H), 3.99 - 3.91 (m, 1H), 3.73 - 3.59 (m, 1H), 3.55 (s, 1.5H), 3.52 (s, 1.5H), 3.49 - 3.37 (m, 1H).	LC/MS: calc'd 565 (MH ⁺), exp 565 (MH ⁺)
108	¹ H NMR (400MHz, METHANOL-d ₄): 8.11 (dd, J = 1.1, 3.1 Hz, 1H), 8.02 - 7.94 (m, 1H), 7.56-7.53 (m, 1H), 7.31 (dd, J = 2.6, 8.7 Hz, 1H), 7.21 - 7.07 (m, 1H), 6.25 (s, 1H), 4.47 - 4.26 (m, 2H), 4.18 - 3.91 (m, 3H), 3.80 - 3.61 (m, 5H), 3.59 - 3.43 (m, 1H), 2.91 - 2.73 (m, 1H), 2.60 - 2.41 (m, 1H).	LC/MS: calc'd 513 (MH ⁺), exp 513 (MH ⁺)
109	¹ H NMR (400MHz, DMSO-d ₆): 9.87 (s, 1H), 7.96 (dd, J = 3.0, 16.8 Hz, 2H), 7.51 - 7.34 (m, 2H), 7.18 (dt, J = 2.6, 8.5 Hz, 1H), 6.04 (s, 1H), 4.23 (d, J = 17.3 Hz, 1H), 4.13 (d, J = 17.4 Hz, 1H), 3.51 (s, 3H), 3.50 (br, 1H), 2.79 - 2.60 (m, 1H), 2.45 - 2.11 (m, 7H), 1.54 (d, J = 13.8 Hz, 1H), 1.29 (dd, J = 3.5, 14.1 Hz, 1H).	LC/MS: calc'd 569 (MH ⁺), exp 569 (MH ⁺)
110	¹ H NMR (400MHz, METHANOL-d ₄): 8.03 (d, J = 3.0 Hz, 1H), 7.92 (d, J = 3.0 Hz, 1H), 7.54 (dd, J = 6.0, 8.8 Hz, 1H), 7.30 (dd, J = 2.6, 8.7 Hz, 1H), 7.12 (dt, J = 2.5, 8.4 Hz, 1H), 6.22 (s, 1H), 4.85 (d, J = 17.3 Hz, 1H), 4.50 (d, J = 17.3 Hz, 1H), 4.15 (d, J = 4.8 Hz, 2H), 3.65 (s, 3H), 3.10 - 2.94 (m, 1H), 2.84 - 2.56	LC/MS: calc'd 569 (MH ⁺), exp 569 (MH ⁺)

	(m, 6H), 2.07 (d, J = 14.1 Hz, 1H), 1.81 (d, J = 14.6 Hz, 1H).	
111	¹ H NMR (400MHz, METHANOL-d ₄): 7.95 (d, J = 3.3 Hz, 1H), 7.74 (d, J = 3.0 Hz, 1H), 7.11 - 6.95 (m, 2H), 5.93 (s, 1H), 4.28 (d, J = 3.3 Hz, 2H), 3.62 (s, 2H), 3.56 - 3.48 (m, 1H), 2.86 - 2.63 (m, 2H), 2.61 - 2.33 (m, 8H), 2.32 - 2.20 (m, 2H), 1.76 - 1.66 (m, 1H), 1.40 (dd, J = 3.5, 14.3 Hz, 1H).	LC/MS: calc'd 567 (MH ⁺), exp 567 (MH ⁺)
112	¹ H NMR (400MHz, METHANOL-d ₄): 7.95 (d, J = 3.0 Hz, 1H), 7.73 (d, J = 3.3 Hz, 1H), 7.12 - 6.95 (m, 2H), 5.94 (s, 1H), 4.52 (dd, J = 2.0, 17.8 Hz, 1H), 3.98 (d, J = 17.8 Hz, 1H), 3.62 (s, 3H), 3.41 - 3.36 (m, 1H), 2.81 - 2.62 (m, 2H), 2.60 - 2.29 (m, 7H), 2.28 - 2.12 (m, 2H), 1.74 (d, J = 10.8 Hz, 1H), 1.34 (dd, J = 3.8, 14.1 Hz, 1H).	LC/MS: calc'd 567 (MH ⁺), exp 567 (MH ⁺)
113	¹ H NMR (400MHz, METHANOL-d ₄): 8.00 (d, J = 3.3 Hz, 1H), 7.80 (d, J = 3.0 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.28 - 7.14 (m, 2H), 5.74 (s, 1H), 4.35 - 4.10 (m, 2H), 3.70 (s, 3H), 3.44 (br, 1H), 3.24 (d, J = 11.8 Hz, 1H), 2.84 - 2.65 (m, 2H), 2.55 - 2.30 (m, 4H), 2.29 - 2.16 (m, 1H), 1.69 (d, J = 13.8 Hz, 1H), 1.38 (dd, J = 4.8, 13.8 Hz, 1H).	LC/MS: calc'd 569 (MH ⁺), exp 569 (MH ⁺)
114	¹ H NMR (400MHz, METHANOL-d ₄): 8.00 (d, J = 3.0 Hz, 1H), 7.81 (d, J = 3.0 Hz, 1H), 7.29 - 7.08 (m, 3H), 5.73 (s, 1H), 4.31 - 4.10 (m, 2H), 3.70 (s, 3H), 3.43 (d, J = 6.0 Hz, 1H), 3.28 (d, J = 11.8 Hz, 1H), 2.82 - 2.64 (m, 1H), 2.48 - 2.19 (m, 4H), 2.00 - 1.91 (m, 1H), 1.85 - 1.61 (m, 3H).	LC/MS: calc'd 553 (MH ⁺), exp 553 (MH ⁺)
115	¹ H NMR (400MHz, METHANOL-d ₄): 8.02 (d, J = 3.3 Hz, 1H), 7.80 (d, J = 3.0 Hz, 1H), 7.32 - 7.04 (m, 3H), 5.73 (s, 1H), 4.46 (dd, J = 1.4, 17.7 Hz, 1H), 3.88 (d, J = 17.8 Hz, 1H), 3.70 (s, 3H), 3.29 (br, 2H), 2.76 - 2.61 (m, 1H), 2.45 - 2.18 (m, 4H), 2.02 (d, J = 12.8 Hz, 1H), 1.88 - 1.57 (m, 3H).	LC/MS: calc'd 553 (MH ⁺), exp 553 (MH ⁺)
116	¹ H NMR (400MHz, METHANOL-d ₄) Shift = 7.98 (d, J = 3.3 Hz, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.42 (dd, J = 6.1, 8.7 Hz, 1H), 7.24 (dd, J = 2.5, 8.8 Hz, 1H), 7.06 (dt, J = 2.8, 8.4 Hz, 1H), 6.17 (s, 1H), 4.26 (s, 2H), 3.62 (s, 3H), 3.50 (br. s., 1H), 3.27 (d, J = 12.8 Hz, 1H), 2.96 - 2.85 (m, 1H), 2.69 - 2.49 (m,	LC/MS: calc'd 585 (MH ⁺), exp 585 (MH ⁺)

	3H), 2.33 - 2.15 (m, 3H), 1.94 (d, J = 13.3 Hz, 1H).	
117	¹ H NMR (400MHz, METHANOL-d ₄) Shift = 7.99 (d, J = 3.3 Hz, 1H), 7.75 (d, J = 3.3 Hz, 1H), 7.42 (dd, J = 6.3, 8.8 Hz, 1H), 7.24 (dd, J = 2.8, 8.8 Hz, 1H), 7.05 (dt, J = 2.8, 8.4 Hz, 1H), 6.18 (s, 1H), 4.53 (dd, J = 2.0, 18.1 Hz, 1H), 3.95 (d, J = 17.8 Hz, 1H), 3.62 (s, 3H), 3.40 - 3.35 (m, 1H), 3.31 - 3.23 (m, 1H), 2.95 - 2.80 (m, 1H), 2.53 (s, 3H), 2.44 - 2.33 (m, 1H), 2.24 (d, J = 11.0 Hz, 2H), 1.90 (d, J = 13.8 Hz, 1H).	LC/MS: calc'd 585 (MH ⁺), exp 585 (MH ⁺)
118	¹ H NMR (400MHz, METHANOL-d ₄) 7.95 (d, J = 3.0 Hz, 1H), 7.74 (d, J = 3.3 Hz, 1H), 7.11 - 6.94 (m, 2H), 5.93 (s, 1H), 4.38 - 4.16 (m, 2H), 3.63 (s, 3H), 3.50 (br. s., 1H), 3.26 (br. s., 1H), 2.96 - 2.83 (m, 1H), 2.70 - 2.52 (m, 6H), 2.37 - 2.14 (m, 3H), 1.93 (d, J = 14.6 Hz, 1H).	LC/MS: calc'd 583 (MH ⁺), exp 583 (MH ⁺)
119	¹ H NMR (400MHz, METHANOL-d ₄) ppm 7.95 (d, J = 3.3 Hz, 1H), 7.74 (d, J = 3.3 Hz, 1H), 7.09 - 6.94 (m, 2H), 5.94 (s, 1H), 4.55 (dd, J = 2.4, 17.9 Hz, 1H), 3.97 (d, J = 18.1 Hz, 1H), 3.63 (s, 3H), 3.41 - 3.36 (m, 1H), 3.31 - 3.27 (m, 1H), 2.94 - 2.79 (m, 1H), 2.57 (d, J = 2.5 Hz, 6H), 2.41 (d, J = 14.8 Hz, 1H), 2.25 (br. s., 2H), 1.89 (d, J = 14.6 Hz, 1H).	LC/MS: calc'd 583 (MH ⁺), exp 583 (MH ⁺)
120	¹ H NMR (400MHz, METHANOL-d ₄) 7.96 (d, J = 3.0 Hz, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.36 - 7.10 (m, 3H), 6.23 (s, 1H), 4.28 (s, 2H), 3.62 (s, 3H), 3.50 (br. s., 1H), 3.27 (br. s., 1H), 2.99 - 2.83 (m, 1H), 2.65-2.57 (m, 3H), 2.36 - 2.14 (m, 3H), 1.94 (d, J = 14.1 Hz, 1H).	LC/MS: calc'd 585 (MH ⁺), exp 585 (MH ⁺)
121	¹ H NMR (400MHz, METHANOL-d ₄) 7.96 (d, J = 3.3 Hz, 1H), 7.75 (d, J = 3.0 Hz, 1H), 7.34 - 7.11 (m, 3H), 6.24 (s, 1H), 4.54 (dd, J = 2.1, 17.9 Hz, 1H), 3.97 (d, J = 17.8 Hz, 1H), 3.61 (s, 3H), 3.43 - 3.35 (m, 2H), 2.94 - 2.80 (m, 1H), 2.67 - 2.46 (m, 3H), 2.40 (dd, J = 2.9, 14.2 Hz, 1H), 2.26 (br. s., 2H), 1.97 - 1.85 (m, 1H).	LC/MS: calc'd 585 (MH ⁺), exp 585 (MH ⁺)
122	¹ H NMR (400MHz, METHANOL-d ₄): 7.95 (dd, J = 3.1, 6.1 Hz, 1H), 7.76 (d, J = 2.5 Hz, 1H), 7.48 - 7.39 (m, 1H), 7.24 (dd, J = 2.3, 8.8 Hz, 1H), 7.06 (t, J = 8.4 Hz, 1H), 6.18 (s, 1H), 4.31	LC/MS: calc'd 518 (MH ⁺), exp 518 (MH ⁺)

	- 4.18 (m, 1H), 4.12 (dd, J = 4.0, 17.6 Hz, 1H), 3.87 (dd, J = 4.5, 17.6 Hz, 1H), 3.77 - 3.66 (m, 1H), 3.62 - 3.54 (m, 4H), 3.40 (br. s., 1H), 3.27 (br. s., 1H), 3.08 (t, J = 14.1 Hz, 1H), 2.17 - 2.03 (m, 5H), 1.83 - 1.62 (m, 2H).	
123	¹ H NMR (400MHz, METHANOL-d ₄) 8.03 - 7.94 (m, 1H), 7.79 (d, J = 2.8 Hz, 1H), 7.49 - 7.40 (m, 1H), 7.31 - 7.20 (m, 1H), 7.13 - 7.01 (m, 1H), 6.17 (s, 1H), 4.85 - 4.67 (m, 1H), 4.46 - 4.33 (m, 1H), 4.28 - 4.11 (m, 2H), 4.05 (br. s., 1H), 3.84 (d, J = 11.0 Hz, 2H), 3.68 - 3.60 (m, 3H), 3.24 - 3.11 (m, 1H), 2.98 - 2.68 (m, 2H), 2.61 - 2.50 (m, 1H), 2.42 - 2.26 (m, 1H), 2.25 - 2.06 (m, 1H), 1.78 (br. s., 1H).	LC/MS: calc'd 565 (MH ⁺), exp 565 (MH ⁺)
124	¹ H NMR (400MHz, METHANOL-d ₄) 7.99 (dd, J = 3.1, 9.2 Hz, 1H), 7.74 (dd, J = 3.3, 5.0 Hz, 1H), 7.43 (ddd, J = 2.8, 6.0, 8.8 Hz, 1H), 7.23 (dd, J = 2.5, 8.8 Hz, 1H), 7.11 - 6.98 (m, 1H), 6.17 (d, J = 3.5 Hz, 1H), 4.74 - 4.49 (m, 1H), 4.40 - 4.17 (m, 1H), 4.05 - 3.92 (m, 2H), 3.73 - 3.65 (m, 2H), 3.63 (d, J = 1.5 Hz, 3H), 3.46 - 3.35 (m, 1H), 2.99 - 2.83 (m, 2H), 2.76 (br. s., 1H), 2.67 - 2.43 (m, 2H), 2.36 - 2.23 (m, 1H), 1.49 - 1.36 (m, 1H).	LC/MS: calc'd 565 (MH ⁺), exp 565 (MH ⁺)
125	¹ H NMR (400MHz, DMSO-d ₆) 9.77 (br. s., 1H), 8.04 (d, J = 3.1 Hz, 1H), 7.95 (d, J = 3.1 Hz, 1H), 7.48 - 7.36 (m, 2H), 7.16 (dt, J = 2.6, 8.5 Hz, 1H), 6.04 (s, 1H), 4.55 (dd, J = 2.3, 17.6 Hz, 1H), 4.08 (d, J = 17.4 Hz, 1H), 3.99 - 3.84 (m, 3H), 3.79 (d, J = 11.2 Hz, 1H), 3.52 (s, 3H), 3.19 (d, J = 10.4 Hz, 2H), 2.71 - 2.61 (m, 2H), 2.15 (dd, J = 9.4, 15.8 Hz, 1H), 1.99 - 1.82 (m, 2H).	LC/MS: calc'd 585 (MH ⁺), exp 585 (MH ⁺)
126	¹ H NMR (400MHz, CDCl ₃) 9.80 - 9.66 (m, 1H), 7.88 (d, J = 3.0 Hz, 1H), 7.48 (d, J = 3.1 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.15 (dd, J = 2.6, 8.6 Hz, 1H), 6.92 (dt, J = 2.6, 8.3 Hz, 1H), 6.21 (s, 1H), 4.52 - 4.39 (m, 1H), 4.35 - 4.26 (m, 1H), 4.16 (d, J = 10.3 Hz, 1H), 4.10 - 3.97 (m, 2H), 3.93 - 3.87 (m, 1H), 3.63 (s, 3H), 3.53 - 3.36 (m, 1H), 3.04 - 2.83 (m, 2H), 2.71 (br. s., 1H), 2.42 (dd, J = 9.9, 16.3 Hz, 1H), 2.15 (d, J = 7.7 Hz, 2H).	LC/MS: calc'd 585 (MH ⁺), exp 585 (MH ⁺)

127	¹ H NMR (400MHz, METHANOL-d4) 7.97 (d, J = 3.3 Hz, 1H), 7.75 (d, J = 3.0 Hz, 1H), 7.12 - 6.96 (m, 2H), 5.93 (s, 1H), 4.86 - 4.76 (m, 1H), 4.19 - 3.99 (m, 6H), 3.87 (d, J = 11.0 Hz, 1H), 3.52 - 3.37 (m, 1H), 3.07 (d, J = 10.0 Hz, 1H), 2.82 (dd, J = 3.8, 15.8 Hz, 1H), 2.67 (br. s., 1H), 2.57 (d, J = 2.3 Hz, 3H), 2.26 (dd, J = 9.9, 15.9 Hz, 1H), 2.06 (d, J = 7.5 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H).	LC/MS: calc'd 596 (MH ⁺), exp 596 (MH ⁺)
128	¹ H NMR (400MHz, METHANOL-d4) 7.97 (d, J = 3.3 Hz, 1H), 7.75 (d, J = 3.0 Hz, 1H), 7.09 - 6.98 (m, 2H), 5.93 (s, 1H), 4.54 - 4.32 (m, 2H), 4.17 - 4.04 (m, 4H), 4.01 - 3.81 (m, 2H), 3.51 - 3.37 (m, 1H), 3.01 (d, J = 10.8 Hz, 1H), 2.88 - 2.73 (m, 2H), 2.57 (d, J = 2.5 Hz, 3H), 2.30 (dd, J = 9.8, 15.8 Hz, 1H), 2.13 (d, J = 7.5 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H).	LC/MS: calc'd 596 (MH ⁺), exp 596 (MH ⁺)
129	¹ H NMR (400MHz, METHANOL-d4) 7.98 (d, J = 3.0 Hz, 1H), 7.76 (d, J = 3.3 Hz, 1H), 7.27 (d, J = 1.8 Hz, 2H), 7.21 - 7.10 (m, 1H), 6.24 (s, 1H), 4.86 - 4.73 (m, 1H), 4.20 - 4.12 (m, 1H), 4.11 - 3.99 (m, 5H), 3.88 (d, J = 11.0 Hz, 1H), 3.51 - 3.37 (m, 1H), 3.12 - 3.02 (m, 1H), 2.80 (d, J = 3.8 Hz, 1H), 2.70 (br. s., 1H), 2.33 - 2.20 (m, 1H), 2.06 (d, J = 9.3 Hz, 2H), 1.16 (t, J = 7.0 Hz, 3H).	LC/MS: calc'd 599 (MH ⁺), exp 599 (MH ⁺)
130	¹ H NMR (400MHz, METHANOL-d4) 7.98 (d, J = 3.3 Hz, 1H), 7.76 (d, J = 3.3 Hz, 1H), 7.33 - 7.21 (m, 2H), 7.16 (dd, J = 1.6, 9.2 Hz, 1H), 6.24 (s, 1H), 4.43 (d, J = 8.0 Hz, 2H), 4.16 - 4.00 (m, 4H), 3.98 - 3.82 (m, 2H), 3.53 - 3.36 (m, 1H), 3.02 (d, J = 10.5 Hz, 1H), 2.90 - 2.75 (m, 2H), 2.31 (dd, J = 9.8, 15.8 Hz, 1H), 2.13 (d, J = 7.0 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).	LC/MS: calc'd 599 (MH ⁺), exp 599 (MH ⁺)
131	¹ H NMR (400MHz, METHANOL-d4) 7.98 (d, J = 3.0 Hz, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.27 - 7.16 (m, 2H), 6.17 (s, 1H), 4.82 - 4.72 (m, 1H), 4.43 (d, J = 18.6 Hz, 1H), 4.19 - 3.86 (m, 4H), 3.62 (s, 3H), 3.51 - 3.37 (m, 1H), 3.10 - 2.96 (m, 1H), 2.90 - 2.65 (m, 2H), 2.35 - 2.20 (m, 1H), 2.17 - 2.02 (m, 2H).	LC/MS: calc'd 603 (MH ⁺), exp 603 (MH ⁺)
132	¹ H NMR (400MHz, METHANOL-d4) 7.96 (d, J = 3.3 Hz, 1H), 7.74 (d, J = 3.3 Hz, 1H), 7.03 (d, J = 6.3 Hz, 2H), 5.93 (s, 1H),	LC/MS: calc'd 582 (MH ⁺), exp

	4.55 - 4.44 (m, 1H), 4.42 - 4.33 (m, 1H), 4.16 - 4.01 (m, 2H), 3.89 (s, 2H), 3.63 (s, 3H), 3.51 - 3.36 (m, 1H), 3.00 (d, J = 10.8 Hz, 1H), 2.88 - 2.74 (m, 2H), 2.57 (d, J = 2.3 Hz, 3H), 2.31 (dd, J = 9.8, 15.8 Hz, 1H), 2.13 (d, J = 8.5 Hz, 2H).	582 (MH ⁺)
133	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, 1H), 7.77 (d, 1H), 7.40-7.48 (m, 1H), 7.24 (m, 1H), 7.06 (m, 1H), 6.18 (d, 1H), 4.42-4.53 (m, 1H), 4.10-4.18 (m, 1H), 4.00-4.10 (m, 2H), 3.87-4.00 (m, 3H), 3.65 (d, 3H), 3.41-3.52 (m, 2H), 2.18-2.25 (m, 1H).	LC/MS: exp 506 [M+H] ⁺
134	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.93-8.01 (m, 1H), 7.75 (d, 1H), 7.61 (m, 1H), 7.37-7.45 (m, 1H), 7.32 (m, 1H), 7.16 (m, 1H), 6.19 (s, 1H), 4.62 (d, 1H), 4.23 (d, 1H), 3.96-4.09 (m, 2H), 3.62 (s, 3H), 3.56 (d, 2H), 2.90-3.02 (m, 2H), 2.62-2.71 (m, 1H), 2.49-2.54 (m, 2H), 2.38-2.49 (m, 2H), 1.44-1.57 (m, 2H).	LC/MS: calc'd 576 (MH ⁺), exp 576(MH ⁺)
135	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.02 (d, 1H), 7.92 (d, 1H), 7.35-7.44 (m, 1H), 7.30 (m, 1H), 6.21 (s, 1H), 5.03 (d, 1H), 4.71 (d, 1H), 4.14-4.26 (m, 2H), 3.85 (br. s., 1H), 3.76 (d, 1H), 3.71 (br. s., 1H), 3.67 (s, 3H), 2.68 (m, 6H), 1.90 (d, 2H).	LC/MS: calc'd 567 (MH ⁺), exp 567(MH ⁺)
136	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.04 (d, 1H), 7.93 (d, 1H), 7.44-7.54 (m, 1H), 7.16-7.35 (m, 2H), 5.72 (s, 1H), 5.05 (d, 1H), 4.64 (d, 1H), 4.11-4.26 (m, 2H), 3.77-3.92 (m, 1H), 3.67-3.76 (m, 4H), 3.64 (d, 1H), 2.50-2.76 (m, 5H), 1.88 (d, 2H).	LC/MS: calc'd 549 (MH ⁺), exp 549(MH ⁺)
137	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.94-8.03 (m, 1H), 7.76 (d, 1H), 7.38-7.47 (m, 1H), 7.38-7.47 (m, 1H), 7.24 (m, 1H), 7.06 (m, 1H), 6.17 (s, 1H), 4.49-4.63 (m, 1H), 4.22-4.33 (m, 2H), 4.05-4.18 (m, 2H), 3.66-3.80 (m, 2H), 3.63 (s, 3H), 2.91 (br. s., 1H), 2.39 (br. s., 1H), 1.98-2.31 (m, 5H), 1.63 (br. s., 1H), 1.33-1.36 (m, 3H).	LC/MS: calc'd 609 (MH ⁺), exp 609 (MH ⁺)
138	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.93-8.03 (m, 1H), 7.83 (br. s., 1H), 7.44-7.56 (m, 1H), 7.26 (m, 1H), 7.09 (m, 1H), 6.18 (s, 1H), 5.00 (br. s., 1H), 4.61 (br. s., 2H), 4.20 (m, 5H), 3.71-3.86 (m, 1H), 3.65 (s, 3H), 3.52 (m, 1H), 2.83-2.97 (m, 1H), 2.72-2.83 (m, 1H), 2.60-2.72 (m, 1H), 2.00-2.20 (m, 1H), 1.33-	LC/MS: calc'd 609 (MH ⁺), exp 609(MH ⁺)

	1.51 (m, 1H), 1.30 (m, 3H).	
139	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98 (d, 1H), 7.78 (d, 1H), 7.44 (m, 1H), 7.25 (m, 1H), 7.05 (m, 1H), 6.18 (s, 1H), 4.69 (d, 1H), 4.08-4.26 (m, 3H), 3.87-3.98 (m, 2H), 3.65 (s, 3H), 3.09 (br. s., 1H), 2.94-3.07 (m, 3H), 2.25-2.25 (m, 1H), 2.14-2.25 (m, 1H), 2.00-2.11 (m, 1H).	LC/MS: calc'd 550 (MH ⁺), exp 550 (MH ⁺)
140	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.98-8.08 (m, 1H), 7.90 (d, 1H), 7.07-7.27 (m, 3H), 6.10 (s, 1H), 4.69 (d, 1H), 4.19-4.29 (m, 2H), 4.06-4.19 (m, 3H), 3.95 (m, 2H), 3.19 (d, 1H), 3.09-3.17 (m, 1H), 2.99 (m, 2H), 1.92-2.06 (m, 2H), 1.14-1.26 (m, 3H).	LC/MS: calc'd 548 (MH ⁺), exp 548(MH ⁺)
141	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.04 (d, 1H), 7.91 (d, 1H), 7.42-7.56 (m, 2H), 7.14 (m, 1H), 6.23 (s, 1H), 4.71 (d, 1H), 4.18-4.30 (m, 3H), 4.05-4.17 (m, 2H), 3.96 (m, 2H), 3.19-3.26 (m, 1H), 3.15 (d, 1H), 2.94-3.05 (m, 2H), 1.92-2.08 (m, 2H), 1.19 (m, 3H).	LC/MS: calc'd 609 (MH ⁺), exp 609(MH ⁺)
142	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.95(d, J = 4.0Hz, 1 H), 7.77 (d, J = 4.0Hz, 1H), 7.42 (m,1 H), 7.25 (m, 1H), 7.08 (m, 1 H), 6.16 (s, 1 H), 4.32~4.39 (m, 2H), 4.03-3.98 (d, J = 3H, 1H), 3.84-3.80 (d, J = 16Hz, 1H), 3.60 (s, 3H), 2.80-2.28 (m, 6 H), 2.00(m, 2H).	LC/MS: calc'd 477 (MH ⁺), exp 477 (MH ⁺)
143	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.93(d, J = 4.0Hz, 1 H), 7.74 (d, J = 4.0Hz, 1H), 7.43 (m,1 H), 7.25 (m, 1H), 7.08 (m, 1 H), 6.17 (s, 1 H), 4.47~4.36 (m, 1H), 4.18~4.11 (m, 1H), 3.61 (s, 3H), 3.37 (m, 1H), 3.0 (m, 1 H), 2.74-2.61 (m, 2H), 2.10 (m, 1H), 1.92~1.80(m, 3H).	LC/MS: calc'd 497 (MH ⁺), exp 497 (MH ⁺)
144	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.94(d, J = 4.0Hz, 1 H), 7.76 (d, J = 4.0Hz, 1H), 7.42 (m,1 H), 7.25 (m, 1H), 7.08 (m, 1 H), 6.15 (s, 1 H), 4.37~3.94 (m, 2H), 3.61 (s, 3H), 3.34 (m, 1H), 3.09~2.75 (m, 3 H), 2.36 (m, 1H), 2.04~1.92(m, 3H).	LC/MS: calc'd 497 (MH ⁺), exp 497 (MH ⁺)
145	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.94(d, J = 4.0Hz, 1 H), 7.75 (d, J = 4.0Hz, 1H), 7.42 (m,1 H), 7.25 (m, 1H), 7.08 (m, 1 H), 6.15 (s, 1 H), 4.30~4.14 (m, 3H), 3.87-3.85 (m, 3H),	LC/MS: calc'd 534 (MH ⁺), exp 534 (MH ⁺)

	3.65-3.55 (m, 6H), 3.06-3.04 (d, J = 8Hz, 1H), 2.75-2.72 (d, J = 12Hz, 1 H), 2.05-2.03(d, J = 8Hz, 1H), 1.99 (s, 3H), 1.79-1.76(d, J = 12Hz, 1H), 1.29 (m, 1H).	
146	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.99 (d, J = 4.0Hz, 1 H), 7.77 (d, J = 4.0Hz, 1H), 7.42 (m, 1 H), 7.24 (m, 1H), 7.04 (m, 1 H), 6.17 (s, 1 H), 4.53~4.49 (d, J = 16Hz, 1H), 4.25~4.20 (m, 2H), 4.17~4.14 (m, 2H), 4.06~4.02 (d, J = 16Hz, 1H), 4.00~3.93 (m, 2H), 3.65 (s, 3 H), 3.12 (s, 2H), 3.08 (s, 3H), 2.90 (m, 2H), 2.50 (m, 2H), 2.18~2.15 (t, J1=16Hz, J2=28Hz, 2H), 1.31 (t, J1=8Hz, J2=16Hz, 3H).	LC/MS: calc'd 670 (MH ⁺), exp 670 (MH ⁺)
147	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.99 (d, J = 4.0Hz, 1 H), 7.77 (d, J = 4.0Hz, 1H), 7.42 (m, 1 H), 7.24 (m, 1H), 7.04 (m, 1 H), 6.17 (s, 1 H), 4.52~4.57 (d, J = 16Hz, 1H), 4.19~4.10 (m, 2H), 4.08~4.03 (m, 2H), 3.85~3.80 (m, 2H), 3.83 (s, 3 H), 3.16 (s, 2H), 3.08 (s, 3H), 2.80 (m, 2H), 2.46 (m, 2H), 2.32 (m, 2H), 1.28 (t, J1=4Hz, J2=12Hz, 3H).	LC/MS: calc'd 688 (MH ⁺), exp 688 (MH ⁺)
148	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.09(d, J = 4.0Hz, 1 H), 8.06 (d, J = 4.0Hz, 1H), 7.66 (m, 1 H), 7.30 (m, 1H), 7.10 (m, 1 H), 6.24 (s, 1 H), 4.22 (m, 2H), 3.74 (m, 1H), 3.64 (s, 3H), 2.69-2.60 (m, 1H), 2.33-2.20(m, 2 H), 2.08-2.01(m, 3H).	LC/MS: calc'd 541 (MH ⁺), exp 541 (MH ⁺)
149	¹ H NMR (METHANOL-d ₄ , 400 MHz): 8.03(d, J = 4.0Hz, 1 H), 7.90 (d, J = 4.0Hz, 1H), 7.55 (m, 1 H), 7.28 (m, 1H), 7.10 (m, 1 H), 6.22 (s, 1 H), 4.29~4.15 (m, 2H), 3.75 (m, 1H), 3.63 (s, 3H), 2.62-2.71 (m, 1H), 2.33-2.15(m, 3 H), 2.07-2.02(m, 2H).	LC/MS: calc'd 541 (MH ⁺), exp 541 (MH ⁺)
150	¹ H NMR (400 MHz, METHANOL-d ₄) d ppm 8.04 (d, J = 3.26 Hz, 1 H), 7.95 (d, J = 3.26 Hz, 1 H), 7.15 - 7.38 (m, 3 H), 6.29 (s, 1 H), 4.51 - 4.71 (m, 2 H), 3.92 - 4.23 (m, 4 H), 3.12 (m, 2 H), 2.21 - 2.75(m, 4 H), 1.13(m, 3H).	LC/MS: calc'd 569 (MH ⁺), exp 569 (MH ⁺)
151	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.99(d, J = 4.0Hz, 1 H), 7.82 (d, J = 4.0Hz, 1H), 7.51 (m, 1 H), 7.27 (m, 1H), 7.11 (m, 1 H), 6.17 (s, 1 H), 4.29~4.33 (m, 1H), 4.04~4.10 (m, 2H), 3.75 (m, 1H), 3.63 (s, 3 H), 2.91(m, 1H), 2.54~2.01 (m, 4H).	LC/MS: calc'd 541 (MH ⁺), exp 541 (MH ⁺)
152	¹ H NMR (METHANOL-d ₄ , 400 MHz): 7.95(d, J = 4.0Hz, 1	LC/MS: calc'd

H), 7.78 (d, J = 4.0Hz, 1H), 7.49 (m, 1 H), 7.27 (m, 1H), 7.08 (m, 1 H), 6.18 (s, 1 H), 4.35~4.01 (m, 2H), 4.04~4.10 (m, 2H), 3.86 (m, 1H), 3.61 (s, 3 H), 3.40(m, 1H), 2.40~2.01 (m, 5H).	541 (MH ⁺), exp 541 (MH ⁺)
--	---

Table 2: Anti-HBV activity data of particular compounds in HepG2.2.15 cells

Example No.	EC ₅₀ (μM)	Example No.	EC ₅₀ (μM)	Example No.	EC ₅₀ (μM)
1	0.059	2	0.1143	3	0.4002
4	0.039	5	0.021	6	0.032
7	0.012	9	0.014	10	0.0088
11	0.0066	12	0.566	13	0.27
14	0.013	15	0.043	16	0.015
17	0.004	18	0.020	19	0.004
20	0.035	21	0.020	23	0.3675
24	0.013	25	0.0145	26	0.013
27	0.2541	28	0.015	29	0.0343
30	0.011	31	0.035	32	0.032
33	0.011	34	0.042	35	0.006
36	0.003	38	0.1145	39	0.032
40	0.032	41	0.1326	42	0.0545
43	0.003	45	0.0005	46	0.0866
47	0.2952	48	0.0194	49	0.0172
50	0.0241	51	0.0149	52	0.0179
53	0.0168	54	0.0082	55	0.0223
56	0.0044	57	0.0219	58	0.0114
59	0.0156	60	0.0016	61	0.0048
62	0.007	63	0.0015	64	0.0166
65	0.0118	66	0.0036	67	0.004
68	0.0038	69	0.0031	70	0.0082
71	0.003	72	0.0132	73	0.003
74	0.0109	75	0.0291	76	0.031
77	0.014	78	0.002	79	0.2933
80	0.0017	81	0.0405	82	0.0131

83	0.0086	84	0.0376	85	0.0066
86	0.002	87	0.0394	88	0.0013
89	0.0305	90	0.0035	91	0.0907
92	0.0015	93	0.0289	94	0.0217
95	0.0311	96	0.0068	97	0.1558
98	0.0007	99	0.0126	100	0.2829
101	0.024	102	0.066	103	0.2738
104	0.0048	105	0.0027	106	0.0085
107	0.0021	108	0.0074	109	0.0017
110	0.0443	111	0.0012	112	0.0358
113	0.0091	114	0.0063	115	0.1627
116	0.0073	117	0.0402	118	0.005
119	0.0213	120	0.0096	121	0.033
122	0.0774	123	0.0357	124	0.2956
125	0.0261	126	0.0103	127	0.0161
128	0.0025	129	0.021	130	0.0064
131	0.0057	132	0.0103	133	0.034
134	0.021	135	0.0065	136	0.102
137	0.0032	138	0.0582	139	0.172
140	0.103	141	0.271	142	0.13
143	0.041	144	0.094	145	0.017
146	0.0005	147	0.0009	148	0.0592
149	0.004	150	0.0077	151	0.0295
152	0.0177				

More particular compounds of formula I include the following:

- 9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid;
- 8-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydropyrimidin-4-ylmethyl]-3-oxa-8-aza-bicyclo[3.2.1]octane-6-carboxylic acid;
- (R)-6-(7-Carbamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-sulfamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(2-hydroxy-acetyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid ethyl ester;

(R)-4-(2-Bromo-4-fluoro-phenyl)-6-(7-carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(4-oxo-8-oxa-3,10-diaza-bicyclo[4.3.1]dec-10-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Acetylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methanesulfonylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

2-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-4-fluoro-2-aza-bicyclo[2.1.1]hexane-1-carboxylic acid;

6-(7-Carboxymethyl-3-thia-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(9-oxa-3,4,11-triaza-tricyclo[5.3.1.0*2,6*]undeca-2(6),4-dien-11-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

2-[(1R,5S)-9-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]oxy]acetic acid;

2-[[8-[[4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]oxy]acetic acid;

8-[[4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-6-carboxylic acid;

Methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-[(7-carbamoyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(1R,5S)-7-endo-(sulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

5 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(1R,5S)-7-exo-(methanesulfonamido)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

2-[(1R,5S,6S)-8-[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]acetic acid;

10 Exo-2-[(1S,5R)-9-[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

(1S,5R)-8-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

15 (1R,5S)-8-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

2-[(1R,3S,5S)-8-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

20 2-[(1S,3R,5R)-8-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

25 2-[(1R,3S,5S)-8-[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

30 2-[(1R,3R,5S)-8-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3S,5R)-8-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[[(4S)-4-(3,4-difluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[[(4S)-4-(3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

5 2-[(3R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

10 2-[(3R)-8-[[[(4R)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3S)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

15 2-[(3R)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3S)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(7R)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7S)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

25 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-7-(methanesulfonamido)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

(1S,4R)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylic acid;

(1R,4S)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylic acid;

8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

2-[(7R)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

5 and

2-[(7S)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid.

Compound with favorable pharmacokinetics is more likely to be efficacious and safe. It is
 10 very important for a drug to have a moderate or low clearance and a reasonable half-life, as this
 often leads to a good oral bioavailability and high systemic exposure. Reducing the clearance of
 a compound or drug could reduce the daily dose required for efficacy and therefore give a better
 efficacy and safety profile. As shown in Table 3, compounds of the present invention show low
 human microsomal clearance.

15 Results of human microsomal clearance data of particular compounds are given in Table 3.

Table 3: Human microsomal clearance data of particular compounds

Example No.	CLh (mL/min/Kg)	Example No.	CLh (mL/min/Kg)	Example No.	CLh (mL/min/Kg)
1	3.0	2	3.2	3	0
5	0	6	0.5	8	0
11	9.0	18	1.3	19	4.6
21	4.3	23	7.1	24	2.6
26	3.5	28	0.6	29	1.7
35	6.4	36	7.8	39	7.4
40	1.4	44	7.1	46	4.0
48	4.8	50	1.4	52	2.7
53	7.0	54	6.5	55	0
56	6.1	57	5.0	58	2.1
59	2.1	60	6.4	61	6.3
62	4.6	63	4.1	64	2.6
65	2.8	66	3.2	67	2.9

68	3.5	69	2.4	72	2.8
73	3.6	74	0.5	75	1.0
76	3.3	77	1.3	78	1.9
79	3.5	80	4.6	81	0
82	0	83	1.6	84	0
85	1.3	86	0	87	0
88	0.2	89	0	90	1.5
91	5.1	92	1.7	93	0.2
94	0	95	0	96	1.8
97	0	98	4.5	99	3
100	0	101	0	102	3.0
103	0	109	7.2	110	4.1
111	4.8	113	6.2	114	1.2
115	4.6	116	2.6	117	1.8
118	3.1	120	0	122	7.0
123	3.0	124	4.2	125	0
126	0	127	2.9	128	3.8
129	2.0	130	5.0	131	0
132	2.6	134	1.7	135	4.2
136	5.5	139	5.1	148	2.3
149	3.4	150	3.1		

The aqueous solubility is an important physico-chemical property that plays a significant role in various physical and biological processes. It is desirable to have good solubility which enables good permeability and gastric and intestinal absorption, linear dose proportionality, less PK variability, and easy formulation for PD/PK studies. At different stages of the drug discovery/development process solubility has to be determined and especially in the early phases (lead generation to lead optimization) high throughput methods are needed. Lyophilisation solubility assay (Lysa) is a well adopted high throughput assay to measure compound solubility in industry.

Results of Lysa are given in Table 4.

Table 4: Solubility data of particular compounds

Example No.	Lysa ($\mu\text{g/mL}$)	Example No.	Lysa ($\mu\text{g/mL}$)	Example No.	Lysa ($\mu\text{g/mL}$)
1	540	2	450	3	>678
5	>660	6	>665	10	435
12	>597	13	313	15	233
23	573	24	>621	26	470
28	>655	29	>600	33	100
34	263	39	>610	40	>634
41	>552	42	188	44	>623
46	>685	48	100	50	>724
52	>630	53	163	54	119
55	505	58	>701	59	>732
64	660	65	375	66	390
67	319	68	320	69	203
72	640	73	>654	74	>621
75	>656	76	>706	77	491
78	111	79	>745	80	221
81	>673	82	>628	83	564
84	>643	85	>639	86	149
88	120	90	230	101	580
102	410	103	345	109	107
114	224	115	128	116	495
118	112	120	317	123	>753
124	>753	125	170	126	>605
130	219	131	261	132	330
134	>695	135	533	136	485
139	>610	145	585	148	>655
149	>665				

Based on FDA guidance, in order to support clinical testing in humans, the assessment of acceptable risk-benefit has to be achieved by providing clear evidence of in vitro antiviral

5 activity (EC_{50}) and cytotoxicity (CC_{50}). It is important to establish that an investigational product

has antiviral activity at concentrations that can be achieved in vivo without inducing toxic effects to cells. Furthermore, in a cell culture model, apparent antiviral activity of an investigational product can be the result of host cell death after exposure to the product. The relative effectiveness of the compound in inhibiting viral replication compared to inducing cell death is defined as the selectivity index (CC_{50} value/ EC_{50} value). It is desirable to have a high selectivity index giving maximum antiviral activity with minimal cell toxicity.

Results of CC_{50} and the corresponding selectivity index are given in Table 5.

Table 5: CC_{50} and selectivity index of particular compounds

Example No.	CC_{50} (μ M)	Selectivity index (CC_{50}/EC_{50})	Example No.	CC_{50} (μ M)	Selectivity index (CC_{50}/EC_{50})
7	>100	>8333	10	>100	>11364
11	>100	>15152	14	>100	>7692
17	50	11628	19	58	16571
24	>100	>7692	25	>100	>6897
26	68	5231	28	>100	>9804
33	>100	>9091	35	50	7813
36	38	11875	39	>100	>5848
43	43	14845	45	43	85280
52	>100	>5587	54	60	7300
56	43	9766	58	>100	>8772
59	>100	>6410	60	34	21169
61	53	10942	62	46	6571
63	34	22367	64	>100	>6024
65	71	5980	67	>100	>25000
69	>100	>32258	70	60	7268
71	44	14690	72	>100	>7576
73	72	24083	74	>100	>9174
77	>100	>7143	78	73	36515
80	38	22394	82	>100	>7634
83	65	7558	85	>100	>15152
88	52	39662	104	44	9079

-85-

105	33	12041	107	26	12495
108	74	9953	109	>100	>58824
111	79	65983	113	58	6404
116	>100	>13699	118	45	8960
120	87	9083	126	>100	>9709
128	35	14056	130	69	10830
131	53	9346	135	>100	>15385
137	55	17031	145	>100	>5882
146	>100	>200000	147	>100	>111111
152	>100	>5650			

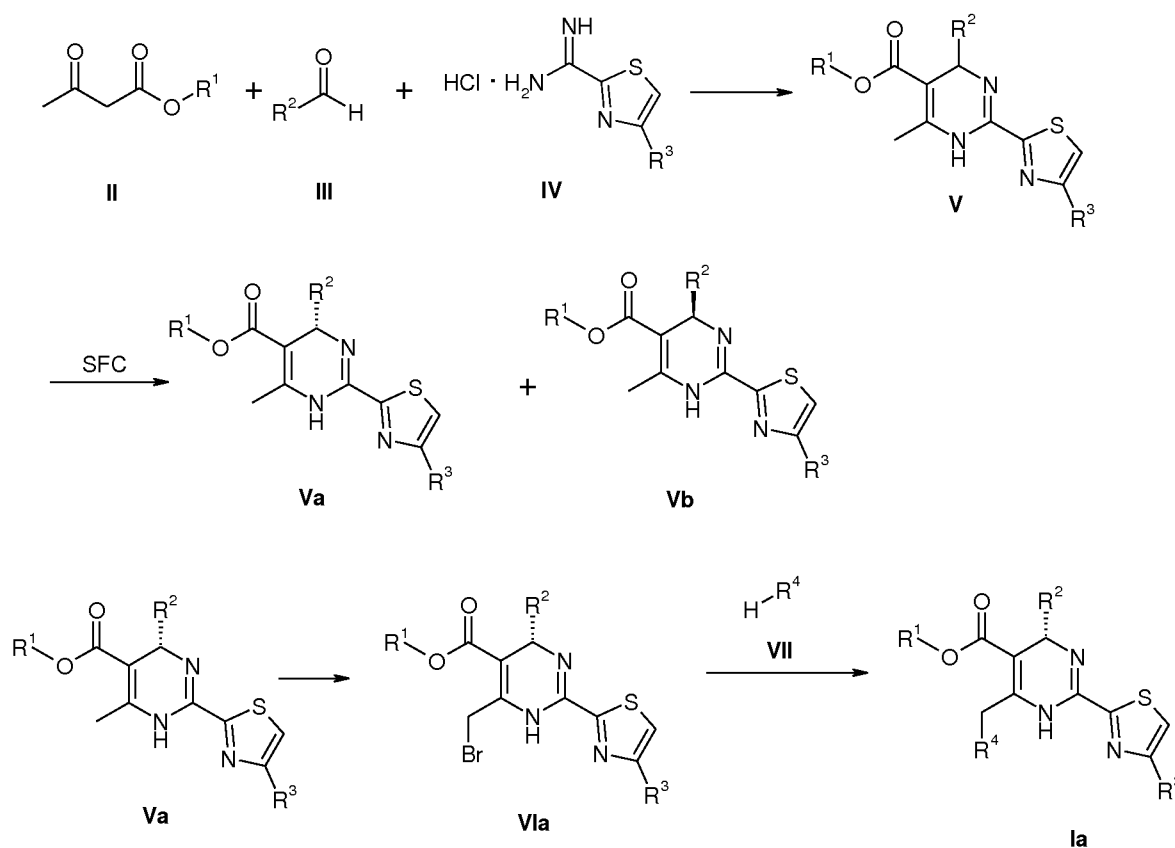
Table 6: Relative induction values of particular compounds to 10 μ M rifampicin

Example No.	% of Positive control (10 μM Rifampicin)
12	21
24	29
26	36
31	25
35	20
38	35
48	17
56	23
66	6.2
68	7.7
69	21
73	21
80	35
88	39
90	37
126	17
135	27

The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds as well as their starting materials are provided in the schemes below and in the examples. All substituents, in particular, R^1 to R^4 are as defined above unless otherwise indicated. Furthermore, and unless explicitly otherwise stated, all reactions, reaction conditions, abbreviations and symbols have the meanings well known to a person of ordinary skill in organic chemistry.

General synthetic route for compound **Ia** (Scheme 1)

Scheme 1



Compound of interest **Ia** can be prepared according to Scheme 1. A one-pot reaction between acetyl acetate **II**, aldehyde **III** and thiazole amidine **IV** gives dihydropyrimidine **V**. (-)-Enantiomer **Va** is then obtained by SFC chiral separation of **V**. The absolute stereochemistry of one specific compound **B1** is determined by X-ray diffraction study (Figure 1) and others are assigned based on comparison of SFC retention time. Bromination of **Va** affords **VIa**. Coupling **VIa** with a suitable bridged amine **VII** gives the compound of interest **Ia**.

Dihydropyrimidine **V** can be prepared from condensation and cyclization sequence of acetyl acetate **II**, aldehyde **III** and thiazole amidine **IV**. The reaction can be carried out in a

suitable alcoholic solvent such as trifluoroethanol in the presence of a base such as potassium acetate under a heating condition over several hours.

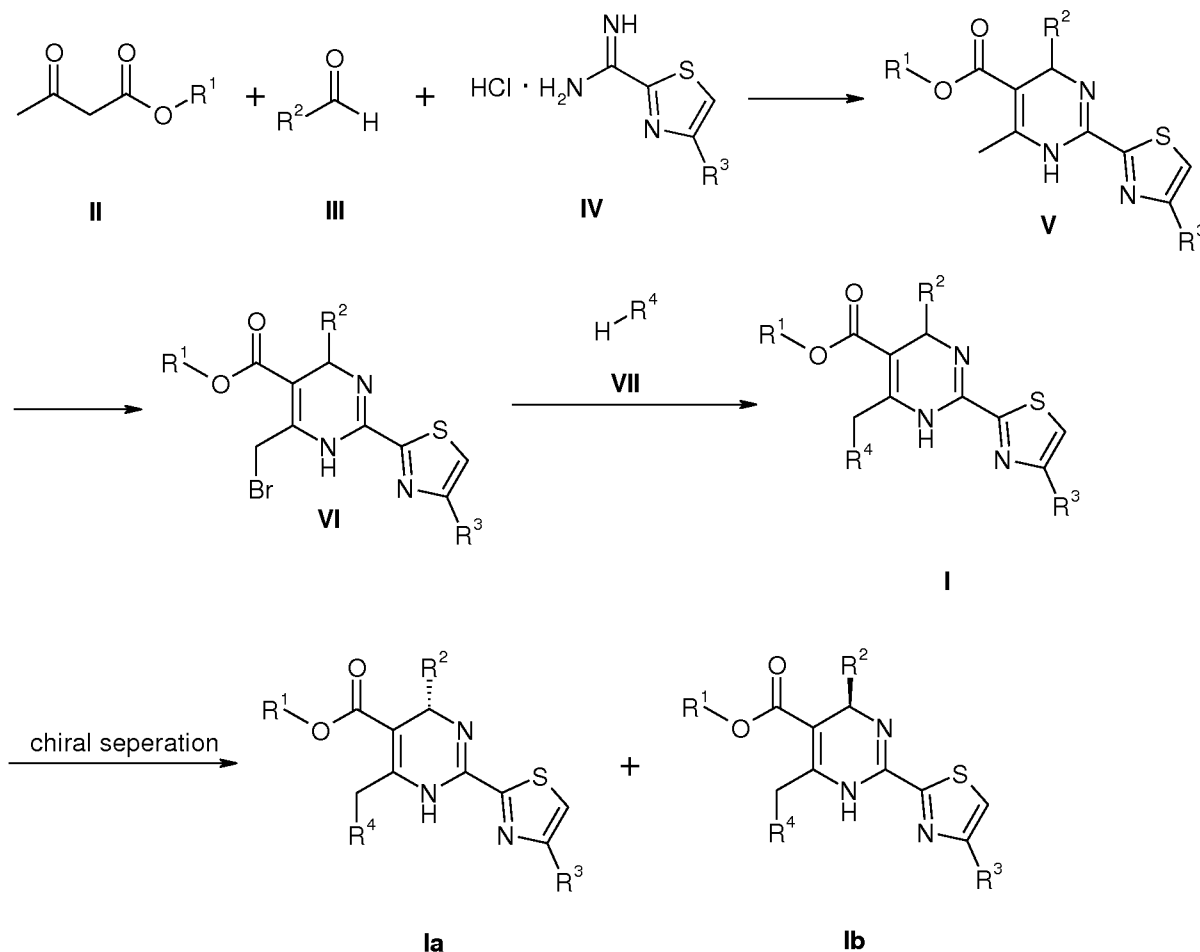
(-)-Enantiomer **Va** is obtained by SFC chiral separation of **V**.

Bromide **VIa** can be prepared by reaction of **Va** with a bromination reagent such as N-bromosuccinimide, in a suitable inert solvent such as carbon tetrachloride at 80-100 degrees Celsius for about 1 hour.

Compound of interest **Ia** can be obtained by coupling bromide **VIa** with bridged amine **VII**. The reaction is typically performed in a suitable solvent such as 1,2-dichloroethane at room temperature over several hours in the presence of an organic base such as N,N-diisopropylethylamine.

An alternative general synthetic route for compounds **I**, **Ia** and **Ib** (Scheme 2)

Scheme 2



Compounds of interest **I**, **Ia** and **Ib** can be prepared according to Scheme 2. Starting with acetyl acetate **II**, aldehyde **III** and thiazole amidine **IV**, dihydropyrimidine **V** can be synthesized through a one-pot condensation reaction. Bromination of Compound **V** affords bromide **VI**.

Coupling bromide **VI** with bridged amine **VII** generates compound of interest **I**. Further chiral separation of **I** affords two enantiomerically pure compounds of interest **Ia** and **Ib**.

Dihydropyrimidine **V** can be prepared from condensation and cyclization sequence of acetyl acetate **II**, aldehyde **III** and thiazole amidine **IV**. The reaction can be carried out in a
 5 suitable alcoholic solvent such as trifluoroethanol in the presence of a base such as potassium acetate under a heating condition over several hours.

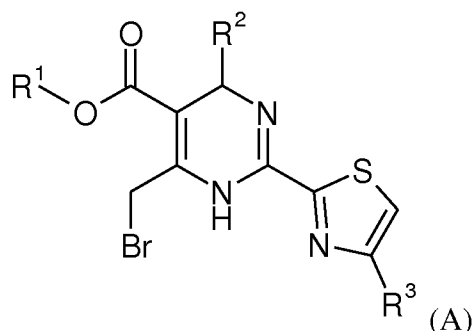
Bromide **VI** can be prepared by reaction of **V** with a bromination reagent such as N-bromosuccinimide in a suitable inert solvent such as carbon tetrachloride at 80-100 degrees Celsius for about 1 hour.

10 Compound of interest **I** can be obtained by coupling bromide **VI** with bridged amine **VII**. The reaction is typically performed in a suitable solvent such as 1,2-dichloroethane at room temperature over several hours in the presence of an organic base such as N,N-diisopropylethylamine.

Compounds of further interest **Ia** and **Ib** are obtained by preparative HPLC
 15 separation of diastereomeric mixture **I**. The stereochemistry of **Ia** is assigned based on the comparison of its analytical data with the compound made by synthetic route A.

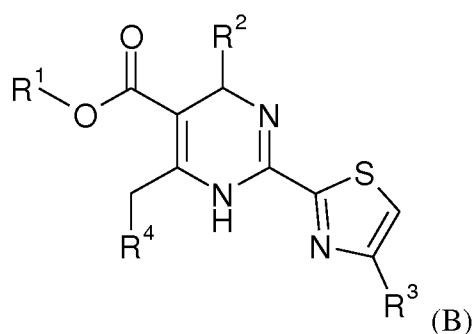
This invention also relates to a process for the preparation of a compound of formula I comprising the reaction of

20 (a) a compound of formula (A)



with bridged amine in the presence of a base;

(b) a compound of formula (B)



under chiral separation condition;

wherein R^1 to R^4 are defined above unless otherwise indicated.

5 In step (a), the base can be for example N,N-diisopropylethylamine.

A compound of formula I when manufactured according to the above process is also an object of the invention.

10 PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

The invention also relates to a compound of formula I for use as therapeutically active substance.

Another embodiment provides pharmaceutical compositions or medicaments containing
 15 the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of formula I may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a
 20 galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula I is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula I are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

25

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular human being treated, the clinical condition of the individual patient, the

cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The “effective amount” of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to the suppression of serum HBV DNA levels, or HBeAg seroconversion to HBeAb, or HBsAg loss, or normalization of alanine aminotransferase levels and improvement in liver histology. For example, such amount may be below the amount that is toxic to normal cells, or the human as a whole.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01 to 100 mg/kg, alternatively about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, contain from about 0.1 to about 1000 mg of the compound of the invention.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers,

stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 0.1 mg to 1000 mg of the compound of the invention compounded with about 90 mg to 30 mg anhydrous lactose, about 5 mg to 40 mg sodium croscarmellose, about 5 mg to 30 mg polyvinylpyrrolidone (PVP) K30, and about 1 mg to 10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 5 mg to 400 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of Formula I, or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of Formula I, or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

INDICATIONS AND METHODS OF TREATMENT

The compounds of the invention can inhibit HBV's de novo DNA synthesis and reduce HBV DNA levels. Accordingly, the compounds of the invention are useful for the treatment or prophylaxis of HBV infection.

The invention relates to the use of a compound of formula I for the treatment or prophylaxis of HBV infection.

The use of a compound of formula I for the preparation of medicaments useful in the treatment or prophylaxis diseases that are related to HBV infection is an object of the invention.

The invention relates in particular to the use of a compound of formula I for the preparation of a medicament for the treatment or prophylaxis of HBV infection.

Another embodiment includes a method for the treatment or prophylaxis of HBV infection in a human in need of such treatment, wherein the method comprises administering to said
5 human a therapeutically effective amount of a compound of Formula I, a stereoisomer, tautomer or pharmaceutically acceptable salt thereof.

COMBINATION THERAPY

The compounds of the invention can be used together with interferon, pegylated
10 interferons, Lamivudine, Adefovir dipivoxil, Entecavir, Telbivudine, and Tenofovir disoproxil for the treatment or prophylaxis of HBV.

Brief description of the Figure

Figure 1. X-ray crystal structure of compound **B1**

15

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

20 Abbreviations used herein are as follows:

$[\alpha]_D^{20}$: specific optical rotation at 20 degrees Celsius

ACN acetonitrile

n-BuLi: n-butyl lithium

t-BuOH: tert-butyl alcohol

25 calc'd: calculated

CbzCl: benzyl chloroformate

CC₅₀: concentration results in the death of 50 percent of the cells

CCK-8: cell counting kit-8

CCl₄: carbon tetrachloride

30 CDCl₃: deuterated chloroform

conc. concentrated

m-CPBA m-chloroperbenzoic acid

CLh: hepatic clearance

	CMV:	cytomegalovirus
	DBB:	di-tert-butylbiphenyl
	DIAD:	diisopropyl azodicarboxylate
	DIG:	digoxigenin
5	DIPEA:	N,N-diisopropylethylamine
	DCM:	dichloromethylene
	DAST	N,N'-diethylaminosulfur trifluoride
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
	DMF	N,N-dimethylformamide
10	DMF-DMA	N,N-dimethylformamide dimethyl acetal
	DMP	Dess-Martin periodinane
	eq	equivalent
	FDA:	Food and Drug Administration
	PE:	petroleum ether
15	DMSO:	dimethylsulfoxide
	DMSO-d ₆ :	deuterated dimethylsulfoxide
	DNA:	deoxyribonucleic acid
	EDTA:	ethylenediaminetetraacetic acid
	EtOH:	ethanol
20	EA or EtOAc:	ethyl acetate
	g:	gram
	EC ₅₀ :	half maximal effective concentration
	HAP:	heteroaryldihydropyrimidine
	HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-
25	b]pyridinium 3-oxid hexafluorophosphate	
	HBeAb:	hepatitis B e antibody
	HBeAg:	hepatitis B e antigen
	HBsAg:	hepatitis B surface antigen
	HCl:	hydrogen chloride
30	HPLC:	high performance liquid chromatography
	HPLC-UV:	high performance liquid chromatography with ultraviolet detector
	Hz:	hertz
	IPA:	isopropanol

	LiHMDS:	lithium hexamethyldisilazide
	LCMS	liquid chromatography–mass spectrometry
	ESI	electrospray ionization
	obsd.	observed
5	TBSCl	tert-butyldimethylsilyl chloride
	NFTh	1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane
	bis(tetrafluoroborate)	
	TosMIC	(p-tolylsulfonyl)methyl isocyanide
	PhI(OAc) ₂	(diacetoxyiodo)benzene
10	METHANOL-d ₄ :	deuterated methanol
	MeOH:	methanol
	mg:	milligram
	MHz:	megahertz
	min:	minute
15	mins:	minutes
	mL:	milliliter
	mm:	millimeter
	mM:	millimolar
	mmol:	millimole
20	MS:	mass spectrometry
	MsCl:	methanesulfonyl chloride
	MW:	molecular weight
	NaCl:	sodium chloride
	NADP:	nicotinamide adenine dinucleotide phosphate (oxidized form)
25	NADPH:	nicotinamide adenine dinucleotide phosphate (reduced form)
	Na ₂ SO ₄ :	sodium sulfate
	NaOH:	sodium hydroxide
	NBS:	N-bromosuccinimide
	NMR:	nuclear magnetic resonance
30	PBS:	phosphate buffered saline
	PD:	pharmacodynamics
	PK:	pharmacokinetics
	prep-HPLC:	preparative high performance liquid chromatography

	Prep-TLC:	preparative thin layer chromatography
	rpm:	round per minute
	sat.	saturated
	SFC:	supercritical fluid chromatography
5	SSC:	saline-sodium citrate buffer
	TBAF:	tetrabutylammonium fluoride
	TBAI:	tetrabutylammonium iodide
	TEA:	triethylamine
	Tet:	tetracycline
10	TFA:	trifluoroacetic acid
	THF:	tetrahydrofuran
	Tris:	tris(hydroxymethyl)aminomethane
	p-TsCl:	p- toluenesulfonyl chloride
	μg:	microgram
15	μL:	microliter
	μM:	micromolar
	UV:	ultraviolet detector
	OD:	optical density
	pgRNA:	pre-genomic RNA
20	qPCR:	quantitative polymerase chain reaction

General Experimental Conditions

Intermediates and final compounds were purified by flash chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii) ISCO
 25 combi-flash chromatography instrument. Silica gel brand and pore size: i) KP-SIL 60 Å, particle size: 40-60 μM; ii) CAS registry NO: Silica Gel: 63231-67-4, particle size: 47-60 micron silica gel; iii) ZCX from Qingdao Haiyang Chemical Co., Ltd, pore: 200-300 or 300-400.

Intermediates and final compounds were purified by preparative HPLC on reversed phase column using XBridge™ Prep-C18 (5 μm, OBD™ 30 × 100 mm) column or SunFire™ Prep-
 30 C18 (5 μm, OBD™ 30 × 100 mm) column. Waters AutoP purification System (Column: XBridge™ Prep-C18, 30 × 100 mm, Sample Manager 2767, Pump 2525, Detector: Micromass ZQ and UV 2487, solvent system: acetonitrile and 0.1% ammonium hydroxide in water). For SFC chiral separation, intermediates were separated by chiral column (Daicel chiralpak IC, 5

μm, 30 × 250 mm) column using Mettler Toledo SFC-Multigram III system, solvent system: 95% CO₂ and 5% IPA (0.5% TEA in IPA), back pressure 100bar, detection UV@ 254nm.

LC/MS spectra of compounds were obtained using a LC/MS (WatersTM Alliance 2795-Micromass ZQ), LC/MS conditions were as follows (running time 6 mins):

- 5 Acidic condition: A: 0.1% formic acid in H₂O; B: 0.1% formic acid in acetonitrile;
Basic condition: A: 0.1% NH₃·H₂O in H₂O; B: acetonitrile;
Neutral condition: A: H₂O; B: acetonitrile.

Mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion (MH)⁺.

- 10 NMR Spectra were obtained using Bruker Avance 400 MHz.

The microwave assisted reactions were carried out in a Biotage Initiator Sixty microwave synthesizer.

- 15 A single crystal was mounted in a loop and cooled to 160 K in a nitrogen stream. Data were collected on a Gemini R Ultra diffractometer (Oxford Diffraction, UK) with Cu-K-alpha-radiation (1.54178Å) and processed with the CrysAlis-package. Structure solution and refinement was performed using the ShelXTL software (Bruker AXS, Karlsruhe).

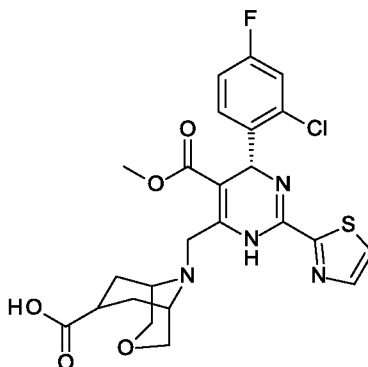
All reactions involving air-sensitive reagents were performed under an argon atmosphere. Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

- 20 The following examples are intended to illustrate the meaning of the present invention but should by no means represent a limitation within the meaning of the present invention:

PREPARATIVE EXAMPLES

Example 1:

- 25 **9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid**



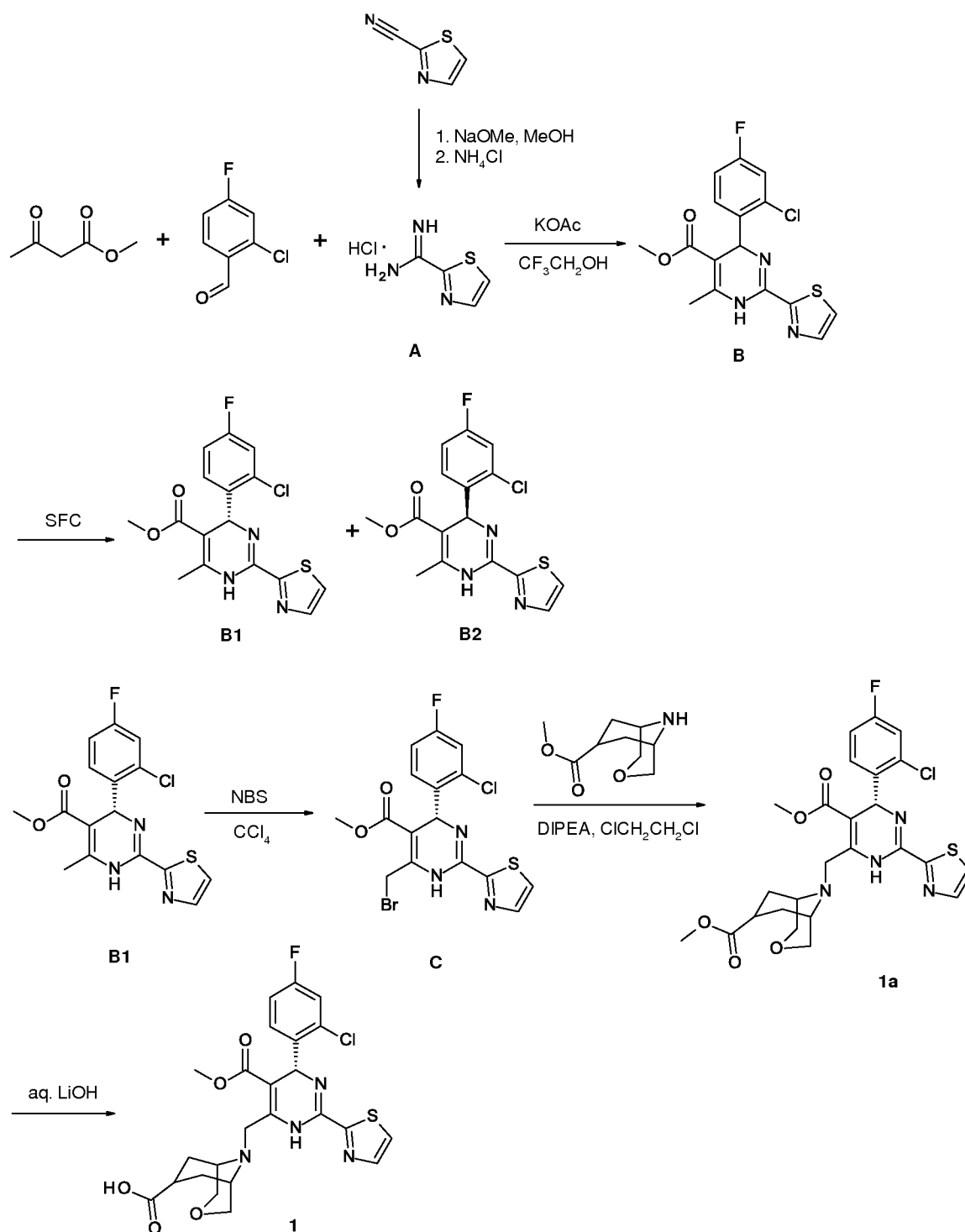
The title compound was prepared according to the general synthetic route shown in Scheme 1. A detailed synthetic route is provided in Scheme 3.

5

10

15

Scheme 3



Preparation of Compound A:

To a stirred solution of thiazole-2-carbonitrile (1.5 g, 14 mmol) in 5 mL of dry MeOH was added dropwise a solution of sodium methoxide (0.74 g, 14 mmol) in 10 mL of dry methanol.

- 5 The reaction mixture was stirred at room temperature until the disappearance of starting material monitored by LC/MS. After that, ammonium chloride (1.5 g, 28 mmol) was added in one portion and the reaction mixture was stirred overnight. The undissolved material was removed by

filtration and the filtrate was concentrated to afford thiazole-2-carboxamidine hydrochloride (Compound A) as a grey solid which was used directly in the next step without further purification. MS: calc'd 128 (MH^+), measured 128 (MH^+).

Preparation of Compound B:

5 To a stirred solution of thiazole-2-carboxamidine hydrochloride (0.13 g, 1.0 mmol), methyl acetoacetate (0.12 g, 1.0 mmol) and 2-chloro-5-fluorobenzaldehyde (0.16 g, 1.0 mmol) in CF_3CH_2OH (8 mL) was added potassium acetate (0.20 g, 2.0 mmol). The reaction mixture was refluxed for 16 hours. After it was cooled to room temperature, the reaction mixture was concentrated and the residue was dissolved in ethyl acetate and then washed with brine. The
10 organic layer was dried over sodium sulfate. The solvent was concentrated, and the residue was purified by column chromatography (ethyl acetate/petroleum ether is from 1/4 to 1/2) to afford 4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound B) as a yellow solid. MS: calc'd (MH^+) 366, measured (MH^+) 366. 1H NMR ($DMSO-d_6$, 400 MHz): δ ppm 9.98 (s, 1H), 7.97 (d, $J = 4.0$ Hz, 1H), 7.90 (d, $J = 4.0$ Hz,
15 1H), 7.41 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.35 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.18 (td, $J = 8.0, 4.0$ Hz, 1H), 5.98 (s, 1H), 3.53 (s, 3H), 2.47 (s, 3H).

Preparation of Compound B1:

The enantiopure (R)-4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound B1) was obtained through SFC (SFC-
20 Multigram; IC: 5×250 mm, 5μ) chiral separation of the stereomixture of 4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-oxazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound B) eluting with a mixed solvent of 85% supercritical CO_2 / 15% EtOH at 100 mL/min rate. The desired (-)-enantiomer B1 has a relatively short retention time. The absolute stereochemistry of (-)-enantiomer B1 was determined by X-ray diffraction study (Figure 1).

25 **Compound B1:** $[\alpha]_D^{20} -55.0$ (c 0.845, MeOH).

Compound B2: $[\alpha]_D^{20} +44.6$ (c 0.175, MeOH).

Preparation of Compound C:

To a stirred solution of (R)-4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (0.37 g, 1.0 mmol) in CCl_4 (5 mL) was added
30 NBS (0.20 g, 1.1 mmol) in portions. After the reaction mixture was stirred at room temperature for 1 hour, the solvent was removed in vacuo and the residue was purified by column chromatography to give (R)-6-bromomethyl-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-

dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound C) as a yellow solid. MS: calc'd 445 (MH⁺), measured 445 (MH⁺).

Preparation of Example 1a:

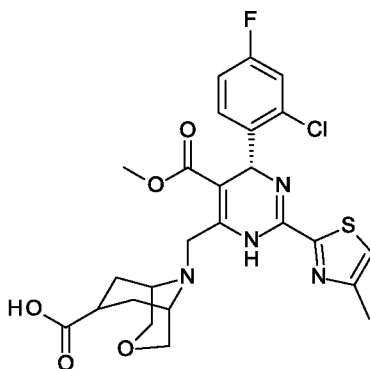
To a stirred solution 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester (90 mg, 0.48 mmol) (PharmaBlock (Nanjing) R&D Co. Ltd, CAS: 1363382-76-6) and (R)-6-bromomethyl-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (104 mg, 0.24 mmol) in ClCH₂CH₂Cl (5 mL) was added DIPEA (0.15 mL, 0.48 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature, then diluted with EtOAc (60 mL), washed with sat. NH₄Cl, sat. NaHCO₃ and brine (20 mL) respectively. The organic layer was dried over Na₂SO₄, concentrated under reduced pressure to give methyl 9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylate as a crude product which was used directly in next step.

Preparation of Example 1:

To a stirred solution of methyl 9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylate in THF (3 mL) was added 0.3 M aq. LiOH (3 mL) at 0 °C. After the reaction mixture was stirred at room temperature for 8 hours, it was neutralized with 1N HCl to pH around 7, then extracted with EtOAc (60 mL). The organic layer was washed with brine (20 mL), dried over Na₂SO₄, concentrated under reduced pressure to give the crude product which was further purified by reverse phase HPLC to give Example 1 as a light yellow solid.

Example 2:

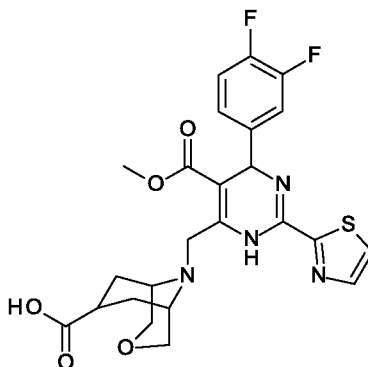
9-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-(4-methyl-thiazol-2-yl)-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid



The title compound was prepared in analogy to Example 1 with the procedure shown in Scheme 3 by using 4-methyl-thiazole-2-carbonitrile instead of thiazole-2-carbonitrile.

Example 3:

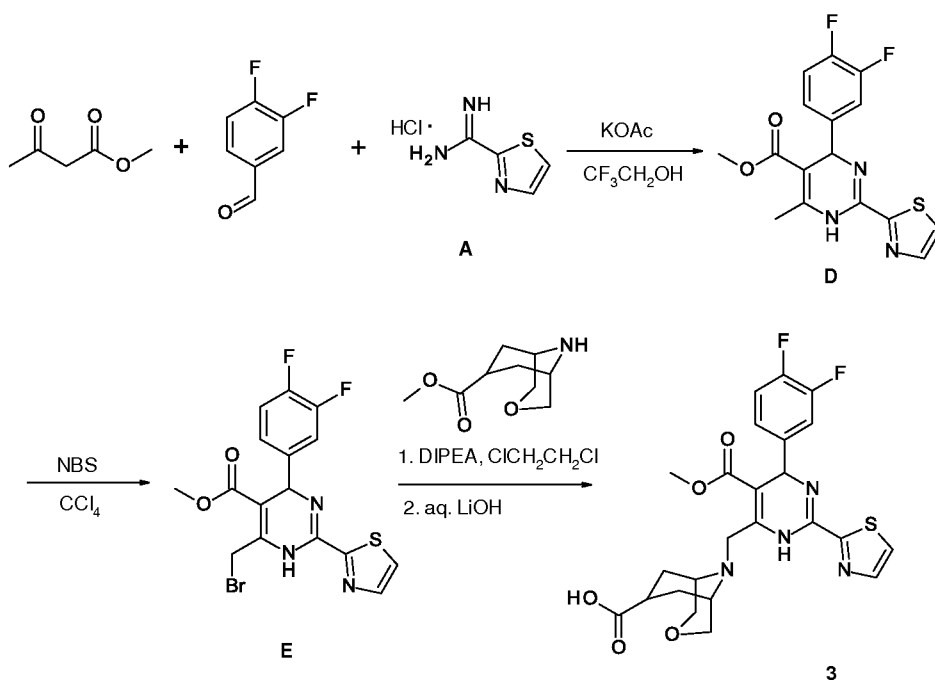
5 9-[6-(3,4-Difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid



The title compounds were prepared according to the general synthetic routes shown in Scheme 2. A detailed synthetic route is provided in Scheme 4.

10

Scheme 4



Example 3 was prepared in analogy to Example 1 with the procedure shown in Scheme 3 by using 4-(3,4-difluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic

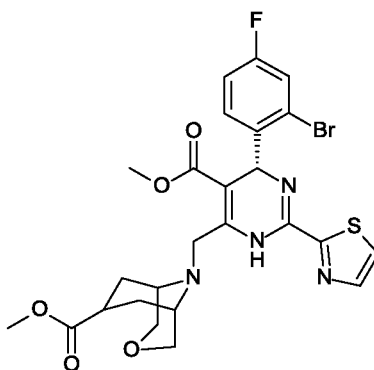
acid methyl ester (Compound **D**) instead of (R)-4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound **B**).

Preparation of 4-(3,4-difluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound **D):**

- 5 Compound **D** was prepared in analogy to Compound **B** with the procedure shown in Scheme 3 by using 3,4-difluoro-benzaldehyde instead of 2-chloro-5-fluorobenzaldehyde.

Example 4:

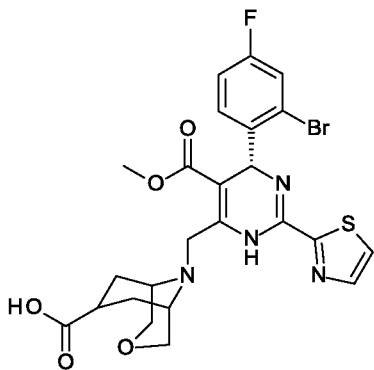
- 10 9-[(R)-6-(2-Bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester



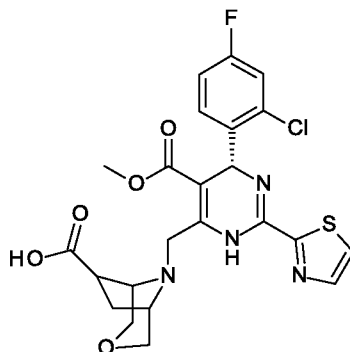
The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 2-bromo-5-fluorobenzaldehyde instead of 2-chloro-5-fluorobenzaldehyde.

- 15 **Example 5:**

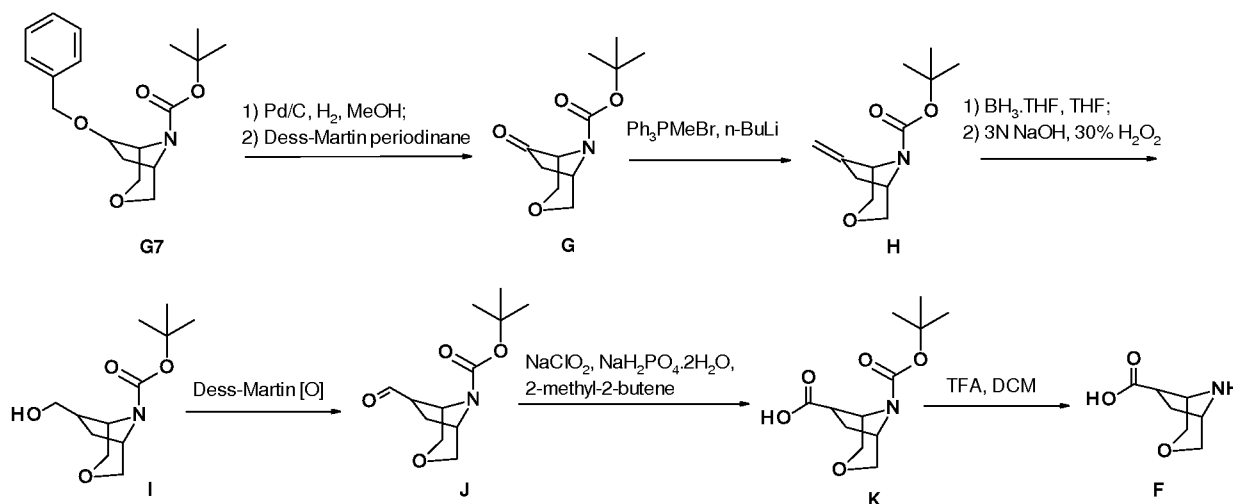
9-[(R)-6-(2-Bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid



- 20 The title compound was prepared in analogy to Example **1** with the procedure shown in Scheme 3 by using 2-bromo-5-fluorobenzaldehyde instead of 2-chloro-5-fluorobenzaldehyde.

Example 6:**8-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-8-aza-bicyclo[3.2.1]octane-6-carboxylic acid**

- 5 The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 3-oxa-8-aza-bicyclo[3.2.1]octane-6-carboxylic acid (Compound **F**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation 3-oxa-8-aza-bicyclo[3.2.1]octane-6-carboxylic acid (Compound F):

- 10 **Step I:** To a solution of 6-benzyloxy-3-oxa-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (**G7**) (160 mg, 0.50 mmol) in MeOH (20 mL) was added Pd on carbon (32 mg). The mixture was stirred at room temperature under H₂ for 8 hours, and then filtered. The solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (10 mL). To the solution was added Dess-Martin periodinane (318 mg, 0.75 mmol) at room temperature. The reaction mixture was stirred for 4 hours, and then quenched with sat. NaHCO₃, then extracted with EtOAc (30 mL) three times. The combined organic layer was washed successively with sat. Na₂CO₃ (15 mL) three times, sat. NH₄Cl and brine. The organic layer was dried over Na₂SO₄. The solvent was removed. The residue was purified by column chromatography to give Compound **G** (100 mg, 88%) as a white solid. MS: calc'd (MH⁺) 228, measured (MH⁺) 228.

Step II: To a solution of methyltriphenylphonium bromide (314 mg, 0.88 mmol) in anhydrous THF (5 mL) was added n-BuLi (1.6 M in hexane, 0.58 mL) at -10 °C under argon atmosphere. The reaction mixture was warmed to room temperature and then stirred for 2 hours. A solution of Compound **G** (100 mg, 0.44 mmol) in anhydrous THF (2 mL) was added to the
5 above mixture at room temperature. The mixture was stirred for additional 3 hours at room temperature, and then quenched with sat. NH₄Cl. The mixture was extracted with EtOAc (30 mL) three times. The combined organic layer was washed with sat. NH₄Cl and brine (20 mL) respectively. The organic layer was dried over Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by column chromatography to give Compound **H** (80 mg,
10 81%) as yellowish oil. MS: calc'd (MH⁺) 226, measured (MH⁺) 226.

Step III: To a solution of Compound **H** (75 mg, 0.33 mmol) in anhydrous THF was added BH₃/THF (1.0 M solution in THF, 0.43 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred for 1.5 hours at 0 °C. To this reaction mixture was added 3N NaOH (0.33 mL, 1.33 mmol) and 30% H₂O₂ (0.33 mL) at 0 °C and the mixture was stirred for 1.5 hours at 0 °C.
15 The reaction mixture was poured into water, and then extracted with EtOAc (30 mL) three times. The combined organic layer was washed with sat. NH₄Cl and brine, and then dried over Na₂SO₄. The solvent was removed under reduced pressure to give Compound **I** (80mg, 98%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): 4.15 (m, 1H), 4.04 (m, 1H), 3.86-3.96 (m, 3H), 3.76 (m, 2H), 3.57 (d, J = 9.8 Hz, 1H), 2.55 (m, 1H), 2.20 (m, 1H), 1.50 (s, 9H).

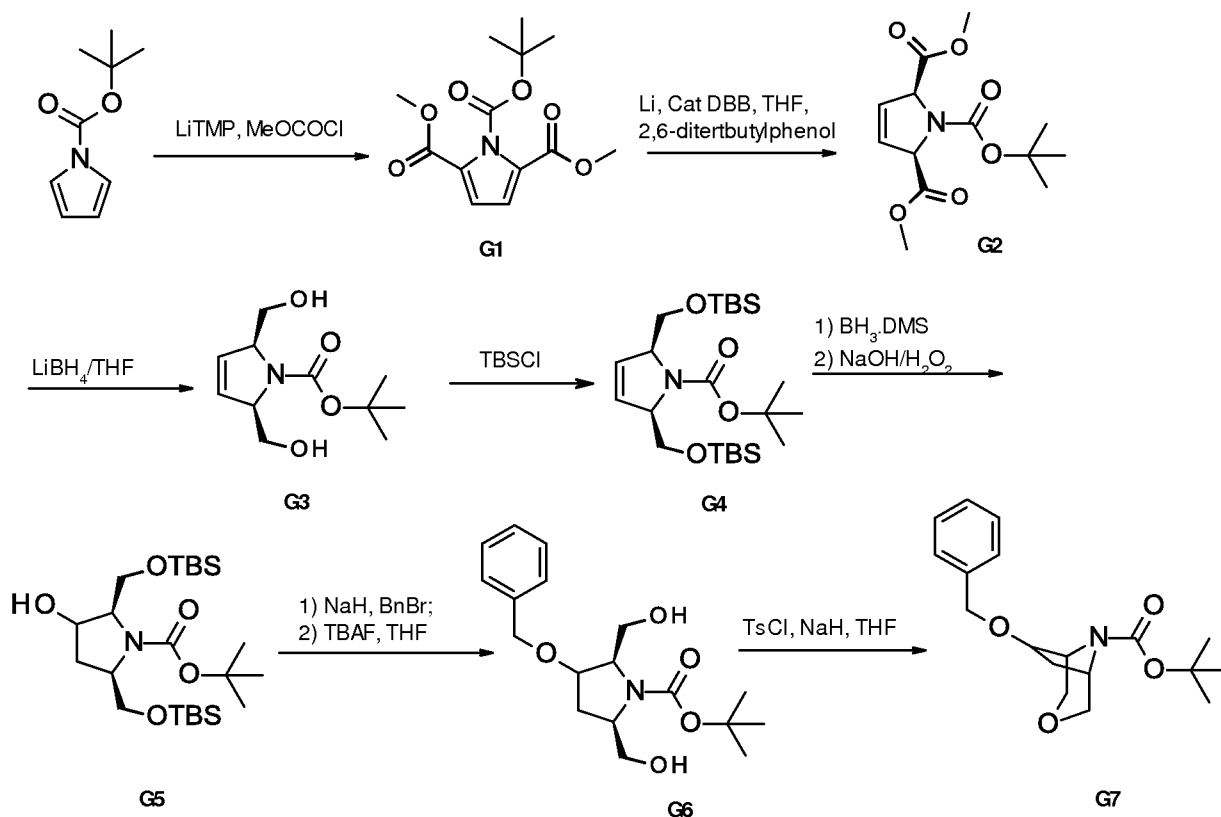
Step IV: To a solution of Compound **I** (80 mg, 0.33 mmol) in CH₂Cl₂ (10 mL) was added Dess-Martin periodinane (210 mg, 0.50 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours, and then diluted with EtOAc (60 mL). The reaction mixture was washed successively with sat. Na₂CO₃ (10 mL) three times, sat. NH₄Cl (20 mL) and brine (20 mL). The organic layer was dried over Na₂SO₄. The solvent was removed under
25 reduced pressure to give Compound **J** (80 mg, 99%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): 9.93 (d, J = 1.8 Hz, 1H), 4.38 (m, 1H), 4.24 (m, 1H), 3.76 (m, 2H), 3.66 (m, 2H), 3.01 (m, 1H), 2.33 (m, 1H), 2.26 (m, 1H), 1.48 (s, 9H).

Step V: To a solution of Compound **J** (80 mg, 0.33 mmol) in t-BuOH (3 mL) was added a-methyl-2-butene (0.75 mL) and a solution of NaClO₂ (278 mg, 3.07 mmol) and NaH₂PO₄/2H₂O
30 (373 mg, 2.39 mmol) in H₂O (3 mL) at room temperature. The reaction mixture was stirred for 2 hours at room temperature. t-BuOH was removed under reduced pressure and aqueous residue was poured into 10% aqueous solution of citric acid. The mixture was extracted with EtOAc (30 mL) three times. The combined organic layer was washed with sat. NH₄Cl and brine, and then

dried over Na_2SO_4 . The solvent was removed under reduced pressure. The residue was further dried under reduced pressure to give Compound **K** (80 mg, 94%) as colorless oil. ^1H NMR (CDCl_3 , 400 MHz): 9.63 (brs, 1H), 4.32 (m, 1H), 4.18 (m, 1H), 4.05 (d, $J = 10.8$ Hz, 1H), 3.68 (m, 2H), 3.64 (d, $J = 10.8$ Hz, 1H), 3.26 (m, 1H), 2.43 (dd, $J = 12.8, 5.5$ Hz, 1H), 2.27 (m, 1H), 1.50 (s, 9H).

Step VI: To a solution of Compound **K** (80 mg, 0.31 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (2 mL) at 0°C . The mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure. The residue was further dried under high-vacuum to give 3-oxa-8-aza-bicyclo[3.2.1]octane-6-carboxylic acid (Compound **F**) (85 mg, 100%) as brown oil. MS (ESI, $[\text{M}+\text{H}]^+$): Calc'd. for $\text{C}_7\text{H}_{12}\text{NO}_3$: 158. Found: 158.

Preparation of literature known intermediate G7 (J. Org. Chem. **2010**, 75, 1643):



Step I: A 1.6 M solution of n-butyllithium in hexanes (46.5 mL, 75 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (12.6 mL, 75 mmol) in THF (100 mL) at -78°C under argon. N-Boc-pyrrole (5 g, 30 mmol) in THF (25 mL) was then added to the mixture. The mixture was stirred for 3 hours, then transferred into methyl chloroformate (3 equivalents, 6.95

mL) via cannula and stirred for a further 30 minutes. Sat. NH_4Cl (20 mL) was added and the mixture was allowed to warm to room temperature. The mixture was then diluted with ether (50 mL), washed with 1 M HCl solution (100 mL) and sat. brine (100 mL). The organic layers were dried over Na_2SO_4 , filtered and concentrated to give the crude product which was purified by
5 flash column chromatography to give 1-tert-butyl, 2,5-dimethyl pyrrole-1,2,5-tricarboxylate (6.60 g, 78%) as a white solid.

Step II: To a Schlenk tube containing DBB (15mg, 0.10mmol) and antibumping granules under argon was added freshly cut lithium wire (98mg, 14mmol). The contents of the tube were then stirred until the lithium had been completely reduced to a powder. The tube was then cooled
10 to -78°C and THF (25mL) was added resulting in a turquoise solution. 1-tert-butyl, 2,5-dimethyl pyrrole-1,2,5-tricarboxylate (1.0g, 3.5mmol) was then added in THF (10 mL) and the resulting red solution was stirred at -78°C until the solution appeared turquoise again. 1,2-Dibromoethane (0.2mL, 7.0mmol) was then added, followed by 2,6-ditertbutylphenol (1.5g, 7.0mmol) in THF (10mL). The mixture was then stirred for a further 2.5 hours before the addition of Sat. NH_4Cl
15 solution (10mL) and the mixture was warmed to room temperature. The mixture was extracted with ether ($2 \times 20\text{mL}$) and the organic layers were combined, then dried over Na_2SO_4 , filtered and concentrated to give the crude product which was purified by flash chromatography to give 1-tert-butyl, 2,5-dimethyl (2S,5R)-2,5-dihydropyrrole-1,2,5-tricarboxylate (800 mg, 80%) as yellow oil.

Step III: To a solution of 1-tert-butyl, 2,5-dimethyl (2S,5R)-2,5-dihydropyrrole-1,2,5-tricarboxylate (6.6 g, 23.1 mmol) in THF (100 mL) was added slowly a LiBH_4 solution (2 M in THF, 34.7 mL, 69.4 mmol) at 0°C . The resulting mixture was stirred at room temperature for 3 hours and then cooled to 0°C . HCl solution (1 M, 30 mL) was added to the reaction mixture and the reaction was stirred for 10 minutes before being diluted with EtOAc. The organic layer was
25 separated, and the aqueous phase was extracted with EtOAc. Combined organic phases were washed with water and brine and dried over Na_2SO_4 . The organic solvent was removed to give the crude product, which was purified by flash chromatography on silica gel to give tert-butyl (2R,5S)-2,5-bis(hydroxymethyl)-2,5-dihydropyrrole-1-carboxylate (3.8 g, 72%). ^1H NMR (CDCl_3 , 300 MHz): 5.77 (d, 2H, $J = 3.0$ Hz), 4.70 (s, 1H), 4.59 (s, 1H), 4.06 (d, 1H, $J = 11.3$
30 Hz), 3.97 (d, 1H, $J = 11.3$ Hz), 3.66 (m, 2H), 1.49 (s, 9H).

Step IV: To a solution of tert-butyl (2R,5S)-2,5-bis(hydroxymethyl)-2,5-dihydropyrrole-1-carboxylate (3.57 g, 15.6 mmol) in DMF (15 mL) were added TBSCl (5.16 g, 34.3 mmol) and imidazole (3.18 g, 46.7 mmol). The mixture was heated at 80°C for 30 minutes, then cooled to

room temperature. The mixture was taken up in water (50 mL) and EtOAc (50 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried over Na₂SO₄. The organic solvent was removed to give the crude product, which was purified by flash chromatography on silica gel to give the tert-butyl (2R,5S)-2,5-diethyl-2,5-dihydropyrrole-1-carboxylate (7.12 g, 98%). ¹H NMR (CDCl₃, 300 MHz): 5.85 (d, 2H, J = 3.0 Hz), 4.50 (s, 1H), 4.36 (s, 1H), 3.85 (m, 2H), 3.47 (t, 1H, J = 8.0 Hz), 3.35 (t, 1H, J = 8.7 Hz), 1.43 (s, 9H), 0.85 (s, 9H), 0.84 (s, 9H), 0.00 (s, 12H).

Step V: To a solution of tert-butyl (2R,5S)-2,5-diethyl-2,5-dihydropyrrole-1-carboxylate (4.8 g, 10.5 mmol) in THF (50 mL) was added slowly BH₃·DMS solution (2M in THF, 6.97 mL, 13.9 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 hours and then cooled to 0 °C. NaOH solution (5 M, 12.6 mL, 63.2 mmol) was added to the reaction mixture, followed by addition of H₂O₂ (30%, 6.33 mL, 62.0 mmol). The resulting mixture was stirred for 5 hours before diluted with EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried over Na₂SO₄. The organic solvent was removed to give the crude product, which was purified by flash chromatography on silica gel to give the tert-butyl (2R,5S)-2,5-diethyl-3-hydroxy-pyrrolidine-1-carboxylate (3.8 g, 77%). ¹H NMR(CDCl₃, 300 MHz): 4.35 (s, 1H), 4.0-3.46 (m, 5H), 3.33 (m, 1H), 2.22-2.10 (m, 1H), 1.89-1.73 (m, 1H), 1.39 (s, 9H), 0.82 (s, 18H), -0.01 (s, 6H), -0.03 (s, 6H).

Step VI: To a solution of tert-butyl (2R,5S)-2,5-diethyl-3-hydroxy-pyrrolidine-1-carboxylate (2.51 g, 5.3 mmol) in THF (50 mL) was added NaH (60%, 0.423 g, 10.6 mmol). The mixture was stirred at room temperature for 30 minutes, and benzyl bromide (1.085 g, 6.3 mmol) and TBAI (0.195 g, 0.5 mmol) were added. The mixture was stirred at room temperature for 12 hours and quenched by addition of sat. NH₄Cl (20 mL). The mixture was concentrated and the residue was taken up in water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried over Na₂SO₄. The organic solvent was removed to give the crude product, which was purified by flash chromatography on silica gel with give the 3-OBn intermediate (2.9 g, 95%) as colorless oil. To a solution of the 3-OBn intermediate (2.9 g, 5.2 mmol) in THF (50 mL) was added slowly of TBAF solution (1M in THF, 21.8 mL, 21.8 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 6 hours and quenched by addition of sat. NH₄Cl (10 mL). The mixture was concentrated in vacuo, and the residue was treated with water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The

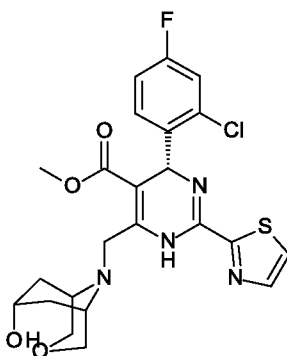
combined organic phases were washed with water and brine and dried over Na₂SO₄. The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel to give tert-butyl (2R,5R)-3-benzyloxy-2,5-

bis(hydroxymethyl)pyrrolidine-1-carboxylate (1.15 g, 63%). ¹H NMR (DMSO-d₆, 300 MHz): 7.31 (m, 5H), 4.82 (t, 1H, J = 5.5 Hz), 4.71 (s, 1H), 4.47 (m, 2H), 4.02 (s, 1H), 3.89-3.73 (m, 2H), 3.54-3.40 (m, 3H), 3.22 (m, 1H), 2.04 (m, 2H), 1.39 (s, 9H).

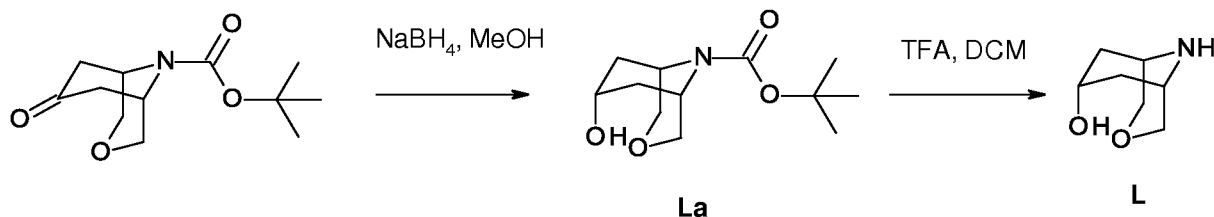
Step VII: To a solution of tert-butyl (2R,5R)-3-benzyloxy-2,5-bis(hydroxymethyl)pyrrolidine-1-carboxylate (1.15 g, 3.4 mmol) in THF (50 mL) was added NaH (60%, 0.409 g, 10.2 mmol). The mixture was stirred at room temperature for 30 minutes and cooled to 0 °C. A solution of p-TsCl (0.65 g, 3.4 mmol) in THF (5 mL) was slowly added to the mixture. The reaction mixture was then stirred at room temperature for 12 hours and quenched by sat. NH₄Cl solution (20 mL). The mixture was concentrated in vacuo, and the residue was taken up with water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried over Na₂SO₄. The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel to give 6-benzyloxy-3-oxa-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (716 mg, 66%) as an off-white solid. ¹H NMR (CDCl₃, 300 MHz): 7.35-7.27 (m, 5H), 4.59-4.43 (m, 2H), 4.38-4.07 (m, 3H), 3.73-3.56 (m, 3H), 3.47 (t, 1H, J = 9.8 Hz), 2.27 (m, 1H), 1.96 (m, 1H), 1.48 (s, 4.5H), 1.44 (s, 4.5H).

Example 7:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-hydroxy-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



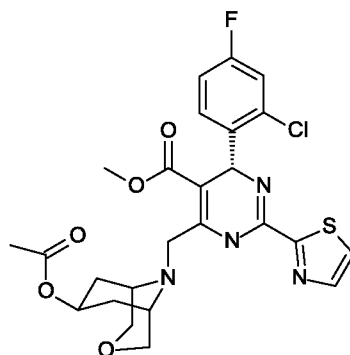
The title compound was prepared in analogy to Example 1a with the procedure shown in Scheme 3 by using 3-oxa-9-aza-bicyclo[3.3.1]nonan-7-ol (Compound L) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of 3-oxa-9-aza-bicyclo[3.3.1]nonan-7-ol (Compound L)

To a stirred solution of 7-oxo-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-carboxylic acid tert-butyl ester (100mg, 0.41 mmol) in MeOH (5 mL) was added NaBH₄ (47 mg, 1.24 mmol) in one portion at room temperature. The mixture was stirred at room temperature overnight, and then quenched with sat. NaHCO₃. The mixture was extracted with EtOAc (20 mL) three times. The organic layer was washed with sat. NaHCO₃ and brine (20 mL) respectively. The organic layer was dried over Na₂SO₄, and then filtered. The solvent was concentrated under reduced pressure to give a crude product **La**, which was dissolved in CH₂Cl₂ (5 mL). Trifluoroacetic acid (2 mL) was added to the solution dropwise at 0 °C. After being stirred at room temperature for 2 hours, the mixture was concentrated under reduced pressure. The residue was further dried on high-vacuum to give 3-oxa-9-aza-bicyclo[3.3.1]nonan-7-ol (Compound **L**) which was directly used for next step. MS: calc'd (MH⁺) 144, measured (MH⁺) 144.

Example 8:

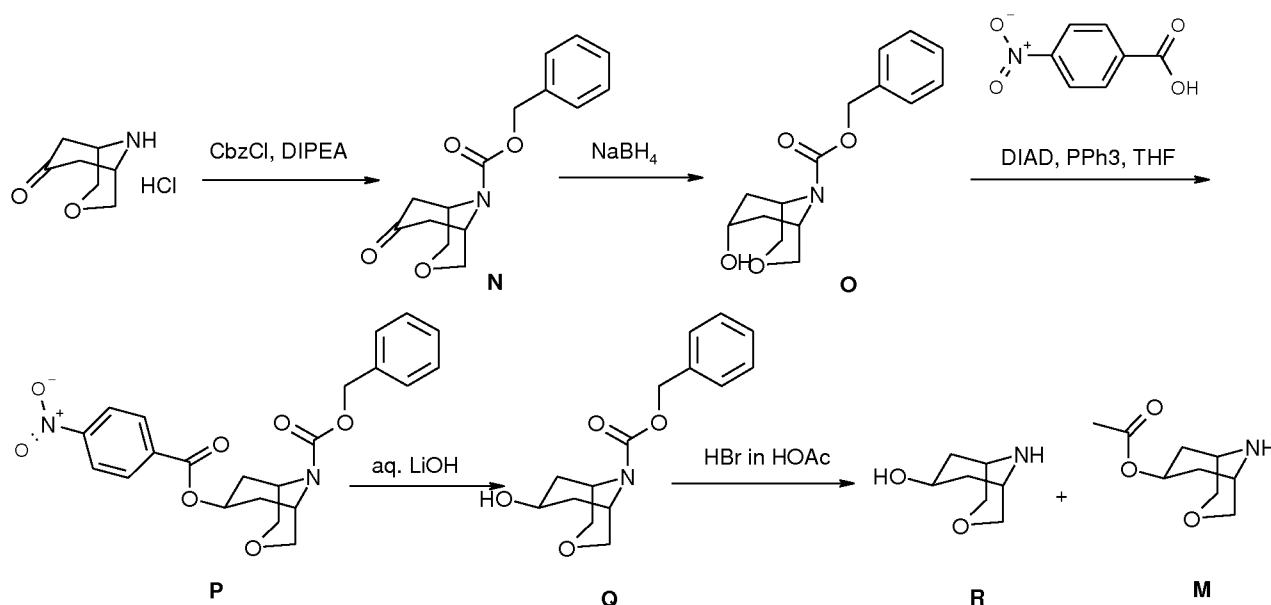
(R)-6-(7-Acetoxy-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluorophenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using acetic acid 3-oxa-9-aza-bicyclo[3.3.1]non-7-yl ester (Compound **M**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of acetic acid 3-oxa-9-aza-bicyclo[3.3.1]non-7-yl ester (Compound M):

-110-



Step I: To a solution of 3-oxa-9-aza-bicyclo[3.3.1]nonan-7-one (PharmaBlock (Nanjing) R&D Co. Ltd, CAS: 1126795-00-3) (1.0 g, 5.6 mmol) and DIPEA (2.9 mL, 17.7 mmol) in CH₂Cl₂ (30 mL) was added CbzCl (0.76 mL, 5.3 mmol) at 0 °C under argon atmosphere. The mixture was stirred at room temperature for 2 hours, and then quenched with sat. NH₄Cl, then extracted with EtOAc (50 mL) three times. The combined organic layer was washed with 1N aq. HCl, sat. NaHCO₃ and brine respectively. The organic layer was dried over Na₂SO₄. The solvent was removed under reduced pressure to give Compound N (1.4 g, 91%).

Step II: To a solution of Compound N (810 mg, 2.9 mmol) in THF (20 mL) was added NaBH₄ (220 mg, 5.8 mmol). The reaction mixture was stirred at room temperature for 3 hours, and then quenched with sat. NH₄Cl. THF was removed under reduced pressure and the residue was extracted with EtOAc (30 mL) three times. The combined organic layer was washed with sat. NH₄Cl, sat. NaHCO₃ and brine respectively, and then dried over Na₂SO₄. The solvent was concentrated to give Compound O (700 mg, 87%) as a white solid. ¹H NMR (CDCl₃, 400MHz): 7.39-7.32 (m, 5H), 5.45 (d, 1H), 5.15 (s, 2H), 4.21-4.11 (m, 2H), 3.89-3.72 (m, 4H), 2.23-2.12 (m, 2H), 1.87-1.82 (m, 2H).

Step III: To a solution of Compound O (300 mg, 1.1 mmol), 4-nitrobenzoic acid (181 mg, 1.1 mmol) and PPh₃ (578 mg, 2.2 mmol) in anhydrous THF (5.0 mL) was added DIAD (445 mg, 2.2 mmol) under argon. The reaction mixture was stirred at room temperature for 16 hours. The solvent was removed and the residue was purified by Prep-TLC (DCM/MeOH = 30/1) to give Compound P (230 mg, 50%) as a white solid. ¹H NMR (CDCl₃, 400 MHz): 8.28 (d, 2H), 8.17 (d,

-111-

2H), 7.38-7.31 (m, 5H), 6.22-6.17 (m, 1H), 5.19 (s, 2H), 4.33 (s, 1H), 4.25 (s, 1H), 3.93-3.85 (m, 2H), 3.74-3.70 (m, 2H), 2.34-2.29 (m, 2H), 1.98-1.88 (m, 2 H).

Step IV: To a solution of Compound **P** (230 mg, 0.54 mmol) in THF (3 mL) was added aq. LiOH (1.0 M, 3.0 mL). The reaction mixture was stirred at room temperature for 2 hours, and then diluted with EtOAc (80 mL). The organic layer was washed successively with sat. Na₂CO₃ (10 mL) three times sat. NH₄Cl (20 mL) and brine (20 mL). The organic layer was dried over Na₂SO₄, and then concentrated to give Compound **Q** (89 mg, 60%) as a white solid. ¹H NMR (CDCl₃, 400 MHz): 7.40-7.31 (m, 5H), 5.16 (s, 2H), 4.91-4.86 (m, 1H), 4.23 (s, 1H), 4.16 (s, 1H), 3.83-3.65 (m, 4H), 2.15-2.09 (m, 2H), 1.74-1.69 (m, 2 H).

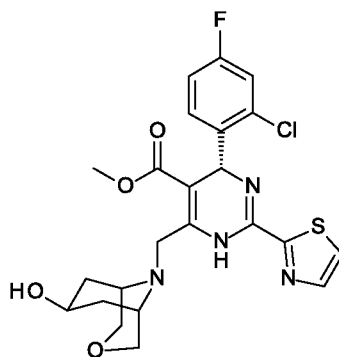
Step V: The crude Compound **Q** was dissolved in HBr/HOAc (33 wt.%, 3 mL). The mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and further dried on high-vacuum to give 3-oxa-9-aza-bicyclo[3.3.1]nonan-7-ol (Compound **R**) and 3-oxa-9-aza-bicyclo[3.3.1]non-7-yl ester (Compound **M**) which were directly used for next step.

Compound **R**: MS: calc'd (MH⁺) 144, measured (MH⁺) 144.

Compound **M**: MS: calc'd (MH⁺) 186, measured (MH⁺) 186.

Example 9:

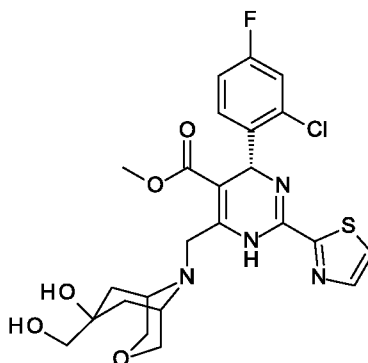
(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-hydroxy-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 3-oxa-9-aza-bicyclo[3.3.1]nonan-7-ol (Compound **R**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

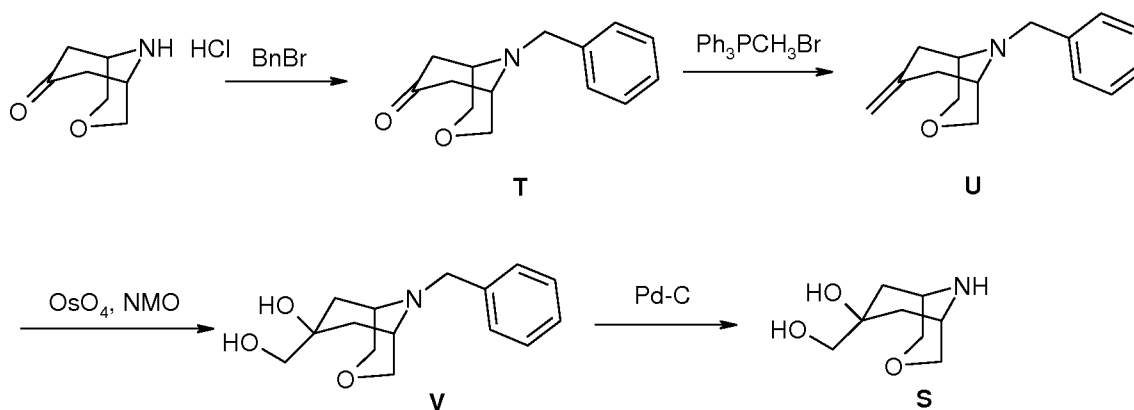
Example 10:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-hydroxy-7-hydroxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



- 5 The title compound was prepared in analogy to Example 1a with the procedure shown in Scheme 3 by using 7-hydroxymethyl-3-oxa-9-aza-bicyclo[3.3.1]nonan-7-ol (Compound S) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of 7-hydroxymethyl-3-oxa-9-aza-bicyclo[3.3.1]nonan-7-ol (Compound S):



- 10 **Step I:** To a stirred solution of 3-oxa-9-azabicyclo[3.3.1]nonan-7-one hydrochloride (1.26 g, 7.08 mmol, cas:1126795-00-3, purchased from PharmaBlock (Nanjing) R&D Co. Ltd,) and potassium carbonate (2.94 g, 14.16 mmol) in DMF (10 mL) was added benzyl bromide (1.33 g, 7.78 mmol) dropwise at room temperature. The resulting mixture was stirred at room temperature overnight, then concentrated and the residue was partitioned between H₂O (5 mL)
- 15 and EtOAc (20 mL). The organic layer was dried, and then concentrated. The residue was purified to give Compound T (1.38 g, 84.2%). ¹H NMR (CDCl₃, 400 MHz): 7.36 (m, 5H), 3.93 (s, 2H), 3.86 (d, J = 11.0, 2H), 3.73 (d, J = 10.8, 2H), 3.18 (d, J = 5.6, 2H), 2.76 (dd, J = 15.9, 5.6 Hz, 2H), 2.35 (d, J = 15.6, 2H) ppm. LC/MS: calc'd 232 (MH⁺), exp 232 (MH⁺).

- 20 **Step II:** A mixture of potassium tert-butoxide (0.292 g, 2.60 mmol) and methyltriphenyl phosphonium bromide (0.927 g, 2.60 mmol) in dry THF (5 mL) was stirred at 0 °C for 30 mins.

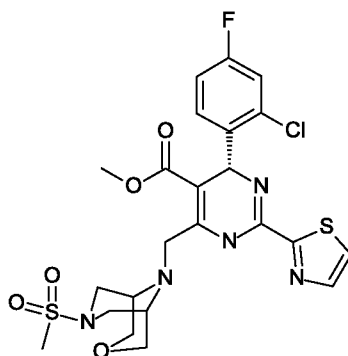
Then a solution of 9-benzyl-3-oxa-9-aza-bicyclo[3.3.1]nonan-7-one (Compound **T**) (0.231 g, 1.00 mmol) in dry THF (2 mL) was added to the reaction mixture. The resulting mixture was allowed to warm to room temperature and then heated at 50 °C overnight. The mixture was concentrated and the residue was partitioned between H₂O (2 mL) and EtOAc (10 mL). The organic phase was dried, and then concentrated. The residue was purified to give Compound **U** (0.098 g, 42.8%). ¹H NMR (CDCl₃, 400 MHz): 7.37 (m, 5H), 4.73 (s, 2H), 3.98 (m, 4H), 3.79 (d, J = 10.8, 2H), 2.83 (m, 4H), 2.29 (m, 2H). LC/MS: calc'd 230 (MH⁺), exp 230 (MH⁺).

Step III: To a stirred solution of 9-benzyl-7-methylene-3-oxa-9-azabicyclo[3.3.1]nonane (Compound **U**) (0.070 g, 0.30 mmol) in acetone (2 mL) and H₂O (0.5 mL) was added N-methylmorpholine-N-oxide (0.140 mg, 0.9 mmol) and osmium tetroxide (0.05 mL, 4% in water, 0.01 mmol) at room temperature. The mixture was stirred at room temperature overnight. The mixture was quenched with saturated Na₂S₂O₃ (10 mL) and then extracted with EtOAc (20 mL × 2). The organic layer was dried, and then concentrated. The residue was purified to give Compound **V** (0.070 g, 88.7%). LC/MS: calc'd 264 (MH⁺), exp 264 (MH⁺).

Step IV: A mixture of 9-benzyl-7-hydroxymethyl-3-oxa-9-aza-bicyclo[3.3.1]nonan-7-ol (Compound **V**) (0.080 g, 0.30 mmol) and Pd/C (20 mg) in MeOH (2 mL) was stirred under H₂ at room temperature overnight. The mixture was filtered and the filtrate was concentrated to give Compound **S** (0.040 g, 77.0%). LC/MS: calc'd 174 (MH⁺), exp 174 (MH⁺).

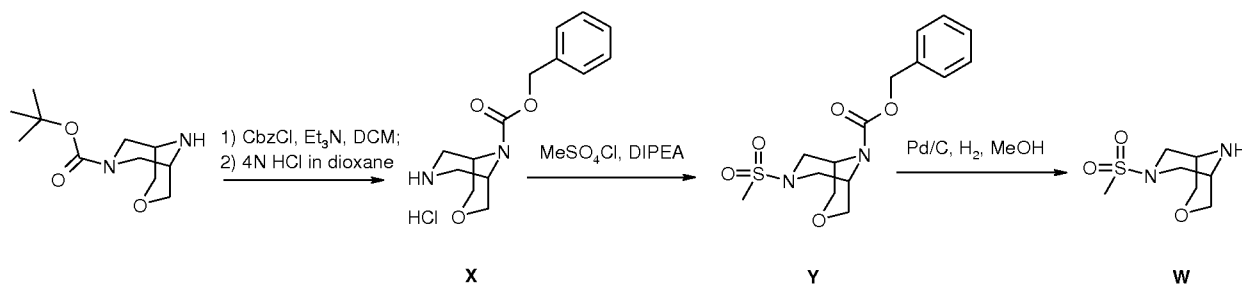
Example 11:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methanesulfonyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 7-methanesulfonyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound **W**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of 7-methanesulfonyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound W)



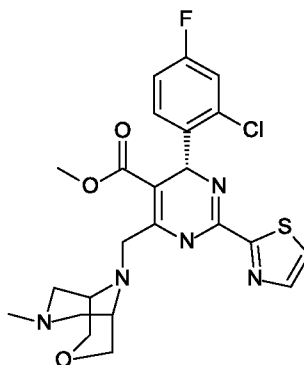
5 To a solution of 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester (WuXi AppTec (Wuhan) Co., Ltd, CAS: 864448-41-9) (173 mg, 0.76 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added DIPEA (195 mg, 1.52 mmol) and CbzCl (155 mg, 0.91 mmol). The reaction mixture was warmed up to room temperature and then stirred for 2 hours. The mixture was quenched with sat. NH₄Cl, and then extracted with EtOAc (60 mL). The organic layer was washed with sat. NH₄Cl, sat. NaHCO₃ and brine (20 mL) respectively, and then dried over Na₂SO₄. The solvent was removed to give a white solid (250 mg, 78%), which was dissolved in CH₂Cl₂ (2 mL). To the solution was added HCl in dioxane (4 M, 2 mL). The reaction mixture was stirred at room temperature for 2 hours. The solvent was removed to give 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound X) (205 mg, 100%) as a white solid. MS: calc'd (MH⁺) 263, measured (MH⁺) 263.

To a solution of 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound X) (100 mg, 0.33 mmol) in CH₂Cl₂ (5 mL) was added DIPEA (0.23 mL, 1.32 mmol) and methanesulfonyl chloride (57 mg, 0.49 mol). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with sat. NH₄Cl, then diluted with EtOAc (60 mL). The mixture was washed with sat. NH₄Cl, sat. NaHCO₃ and brine (20 mL) respectively. The organic layer was dried over Na₂SO₄. The solvent was removed under reduced pressure to give 7-methanesulfonyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound Y) (105 mg, 95%) as yellowish oil. MS: calc'd (MH⁺) 341, measured (MH⁺) 341.

To a solution of the crude Compound Y in MeOH (20 mL) was added 10% Pd on carbon (20 mg). The mixture was stirred under one atmosphere pressure of hydrogen at room temperature. After the reaction was completed, the mixture was filtered and concentrated to give 7-methanesulfonyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound W) (50 mg, 78%) which was directly used for next step. MS: calc'd (MH⁺) 207, measured (MH⁺) 207.

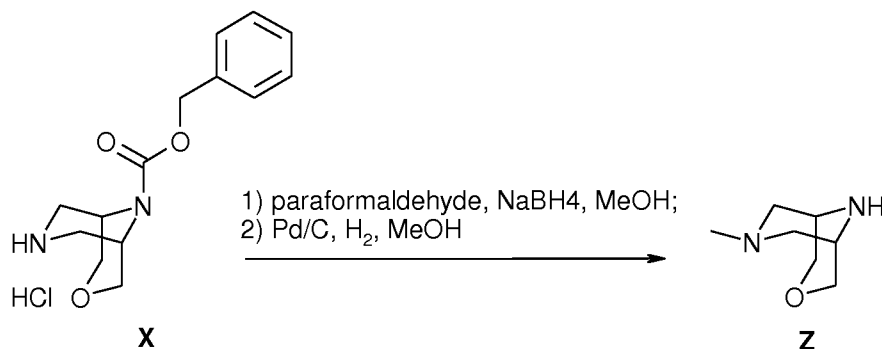
Example 12:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



- 5 The title compound was prepared in analogy to Example 1a with the procedure shown in Scheme 3 by using 7-methyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound **Z**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

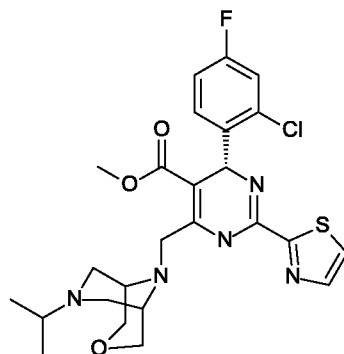
Preparation of 7-methyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound **Z):**



- 10 To a solution of 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound **X**) (84 mg, 0.28 mmol) in MeOH (5 mL) was added paraformaldehyde (41 mg, 1.38 mmol) and NaBH₄ (21 mg, 0.56 mmol). The reaction mixture was refluxed for 16 hours under argon atmosphere, and then quenched with sat. NaHCO₃, then extracted with EtOAc (20 mL) three times. The combined organic layer was washed successively with sat. NH₄Cl, NaHCO₃ and
- 15 brine, and then dried over Na₂SO₄. The solvent was concentrated under reduced pressure. The residue was dissolved in MeOH (20 mL). To the solution was added 10% Pd on carbon (20 mg). The mixture was stirred under one atmosphere pressure of hydrogen at room temperature. After the reaction was completed, the mixture was filtered and concentrated to give the crude 7-methyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound **Z**) (32 mg, 81%) which was directly
- 20 used for next step. MS: calc'd (MH⁺) 143, measured (MH⁺) 143.

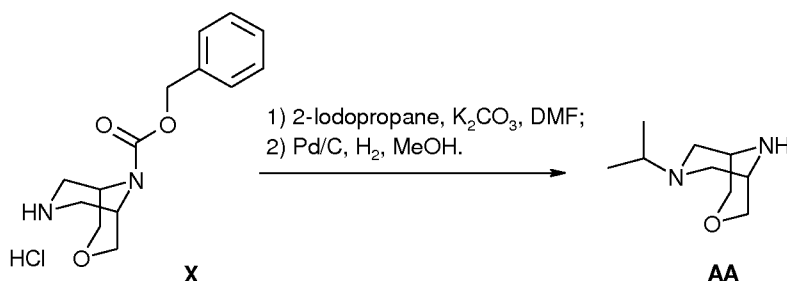
Example 13:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-isopropyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



- 5 The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 7-isopropyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound **AA**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

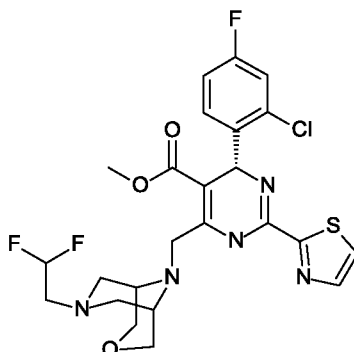
Preparation of 7-isopropyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound AA):



- 10 To a solution of 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound **X**) (100 mg, 0.33 mmol) in DMF (5 mL) was added K_2CO_3 (91 mg, 0.66 mmol) and 2-iodopropane (111 mg, 0.66 mmol). The reaction mixture was heated to 80 °C and stirred for 16 hours. The mixture was diluted with EtOAc (60 mL), and then washed with sat. NH_4Cl , sat. $NaHCO_3$ and brine (20 mL) respectively. The organic layer was dried over Na_2SO_4 , and then
- 15 concentrated to give the crude product which was dissolved in MeOH (20 mL). To the solution was added 10% Pd on carbon (20 mg). The mixture was stirred under one atmosphere pressure of H_2 at room temperature. After the reaction was completed, the mixture was filtered and concentrated to give the crude 7-isopropyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound **AA**) (32 mg, 57%) which was directly used for next step. MS: calc'd (MH^+) 171, measured
- 20 (MH^+) 171.

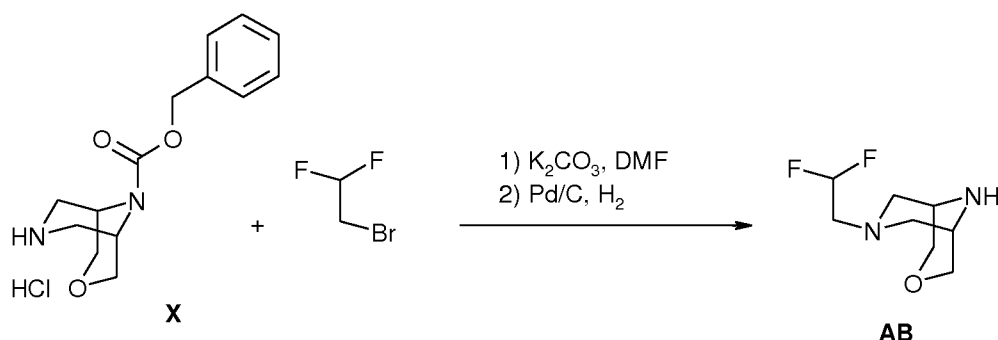
Example 14:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(2,2-difluoro-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



- 5 The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 7-(2,2-difluoro-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound **AB**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of 7-(2,2-difluoro-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound **AB):**



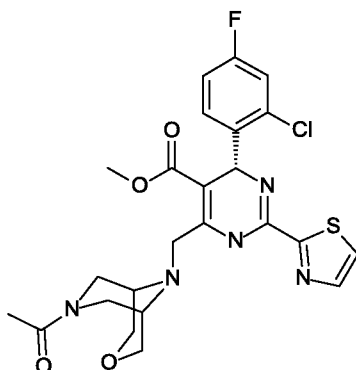
10

To a solution of 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound **X**) (100 mg, 0.33 mmol) in DMF (5 mL) was added K_2CO_3 (91 mg, 0.66 mmol) and 2-iodopropane (95 mg, 0.76 mmol). The reaction mixture was heated to 80 °C and stirred for 16 hours. The mixture was diluted with EtOAc (60 mL), and then washed with sat. NH_4Cl , sat.

- 15 $NaHCO_3$ and brine (20 mL) respectively. The organic layer was dried over Na_2SO_4 , and then concentrated to give the crude product which was dissolved in MeOH (20 mL). To the solution was added 10% Pd on carbon (20 mg). The mixture was stirred under hydrogen atmosphere at room temperature. After the reaction was completed, the mixture was filtered and concentrated to give the crude 7-(2,2-difluoro-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane (Compound **AB**)
- 20 (51 mg, 81%) which was directly used for next step. MS: calc'd (MH^+) 193, measured (MH^+) 193.

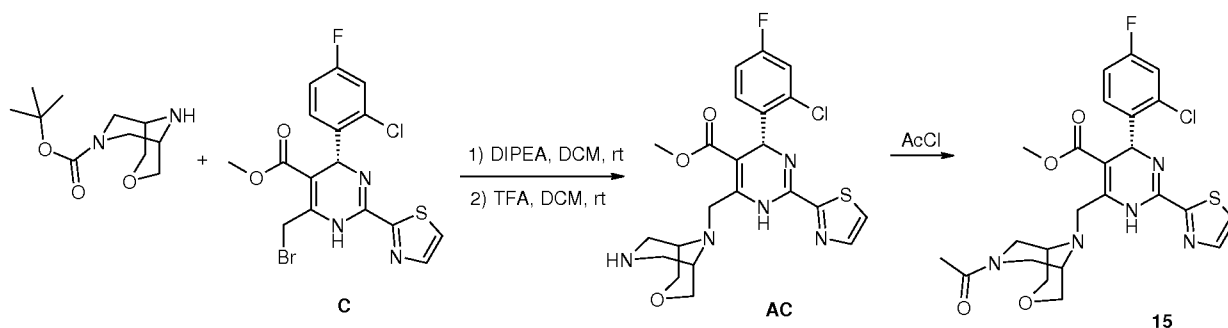
Example 15:

(R)-6-(7-Acetyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluorophenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



5 The title compound was prepared by the procedure shown below (Scheme 5).

Scheme 5



To a solution of (R)-4-(2-chloro-4-fluoro-phenyl)-6-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound AC) (50 mg, 0.1 mmol) and triethylamine (0.042 mL, 0.3 mmol) in CH₂Cl₂ (5 mL) was added acetyl chloride (16 mg, 0.2 mmol) dropwise at ice-bath. The mixture was stirred at 0 °C for 2 hours. The mixture was concentrated in vacuo. The residue was extracted with ethyl acetate (20 mL × 2) and then washed with saturated aqueous sodium bicarbonate solution (20 mL × 2). The organic layer was dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue was purified by prep-HPLC to afford (R)-6-(7-acetyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Example 15) as a light yellow solid (45 mg).

Preparation of (R)-4-(2-chloro-4-fluoro-phenyl)-6-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound AC):

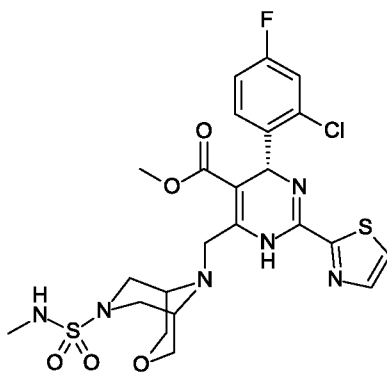
To a mixture of 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester (171 mg, 0.75mmol) and DIPEA(0.45 mL, 2.5 mmol) in CH₂Cl₂ (10 mL) was added (R)-6-bromomethyl-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester(222 mg, 0.5 mmol). The mixture was stirred at room temperature for 16 hours.

5 The mixture was concentrated in vacuo. The residue was purified by flash column chromatography to afford 9-[(R)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester as yellow oil (0.28 g, 94%). MS: calc'd (MH⁺) 592, measured (MH⁺) 592.

To a solution of 9-[(R)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-10 3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester (280 mg, 0.47 mmol) in CH₂Cl₂ (10 mL) was added TFA (2 mL) dropwise in ice-bath. The mixture was stirred at room temperature for 16 hours. The mixture was neutralized with a saturated aqueous sodium bicarbonate solution and then extracted with CH₂Cl₂ (20 mL × 2). The organic layer was washed with saturated aqueous sodium bicarbonate solution (20 mL × 2), and 15 then dried over anhydrous sodium sulfate and then concentrated in vacuo to afford (R)-6-(7-acetyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound AC) as light yellow oil (230 mg, 98%) which was used for next step without further purification. MS: calc'd (MH⁺) 492, measured (MH⁺) 492.

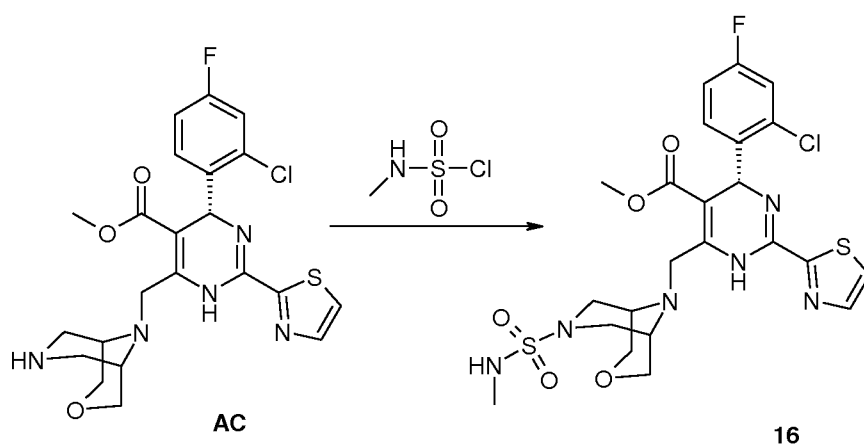
Example 16:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methylsulfamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared by the procedure shown below.

-120-



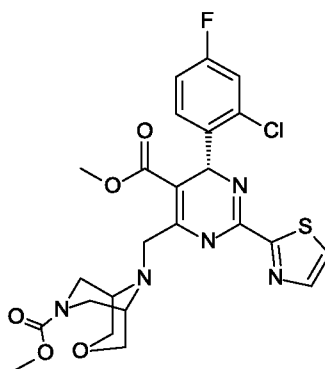
To a solution of (R)-4-(2-chloro-4-fluoro-phenyl)-6-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound **AC**) (50 mg, 0.1 mmol) and triethylamine (0.042 mL, 0.3 mmol) in CH₂Cl₂ (5 mL) was added

5 methylsulfamoyl chloride (26 mg, 0.2 mmol) dropwise in ice-bath. The mixture was stirred at 0°C for 2 hours. The mixture was concentrated in vacuo. The residue was extracted with ethyl acetate (20 mL × 2). The organic layer was washed with saturated aqueous sodium bicarbonate solution (20 mL × 2), and then dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue was purified by preparative HPLC to afford Example **16** as a light yellow

10 solid (35 mg)

Example 17:

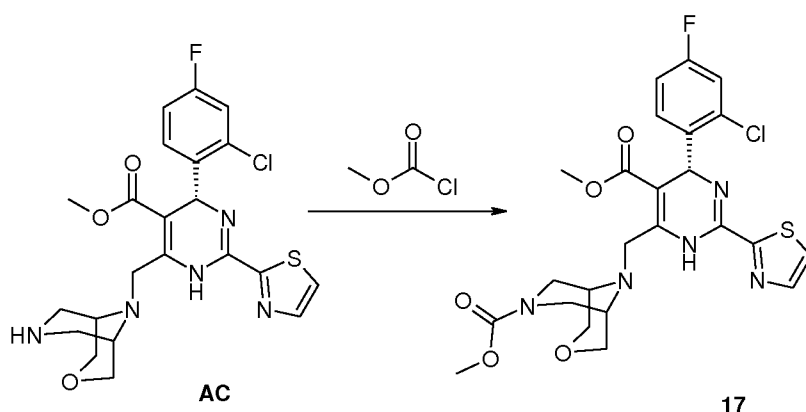
9-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester



15

The title compound was prepared by the procedure shown below.

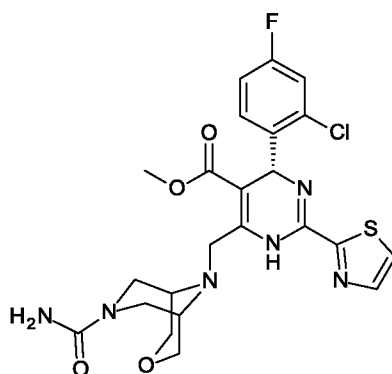
-121-



To a solution of (R)-4-(2-chloro-4-fluorophenyl)-6-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (compound **AC**) (50 mg, 0.1 mmol) and triethylamine (0.042 mL, 0.3 mmol) in CH₂Cl₂ (5 mL) was added methyl chloroformate (19 mg, 0.2 mmol) dropwise in ice-bath. The mixture was stirred at 0°C for 3 hours. The mixture was concentrated in vacuo. The residue was extracted with ethyl acetate (20 mL × 2). The organic layer was washed with saturated aqueous sodium bicarbonate solution (20 mL × 2), and then dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue was purified by preparative HPLC to afford Example **17** as a light yellow solid (19 mg).

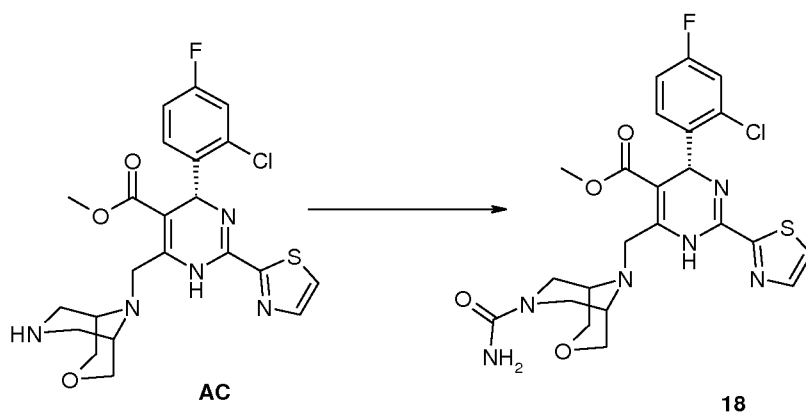
Example 18:

(R)-6-(7-Carbamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluorophenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared by the procedure shown below.

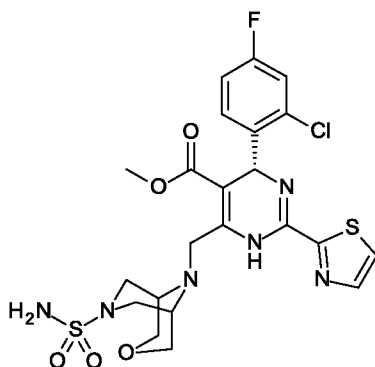
-122-



To a solution of (R)-4-(2-chloro-4-fluoro-phenyl)-6-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound **AC**) (60 mg, 0.12 mmol) and triethylamine (0.17 mL, 1.2 mmol) in CH₂Cl₂ (5 mL) was added
 5 trimethylsilyl isocyanate (55 mg, 0.48 mmol) dropwise in ice-bath. The mixture was stirred at 0°C for 16 hours. The mixture was concentrated in vacuo. The residue was purified by preparative HPLC to afford Example **18** as a light yellow solid (19 mg).

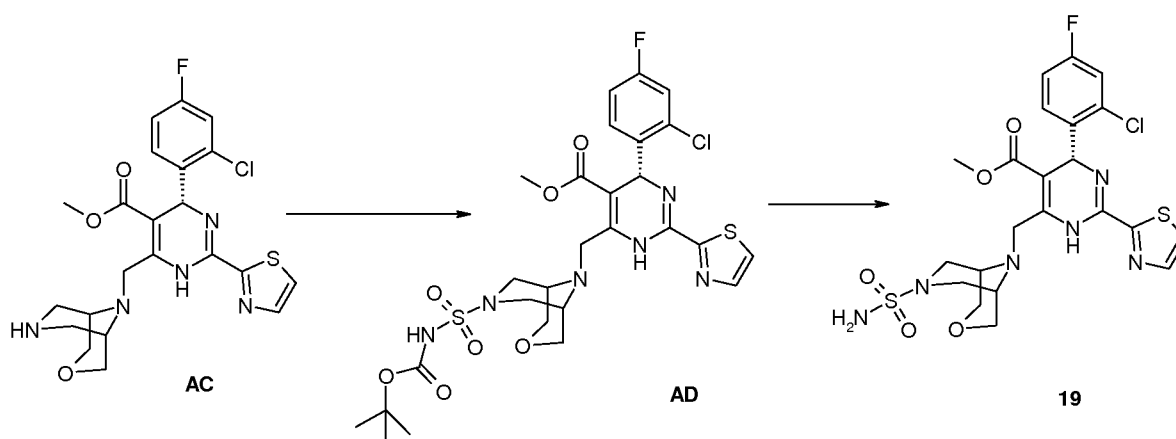
Example 19:

10 **(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-sulfamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester**



The title compound was prepared by the procedure shown below.

-123-



To a solution of Compound **AD** in CH_2Cl_2 (5 mL) was added TFA (0.5 mL) dropwise in ice-bath. The mixture was stirred at room temperature for 2 hours. The mixture was neutralized with a saturated aqueous sodium bicarbonate solution and then extracted with CH_2Cl_2 (20 mL $\times$ 2). The organic layer was washed with saturated aqueous sodium bicarbonate solution (20 mL $\times$ 2), and then dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue was purified by preparative HPLC to afford Example **19** as a light yellow solid (18 mg).

Preparation of Compound **AD**:

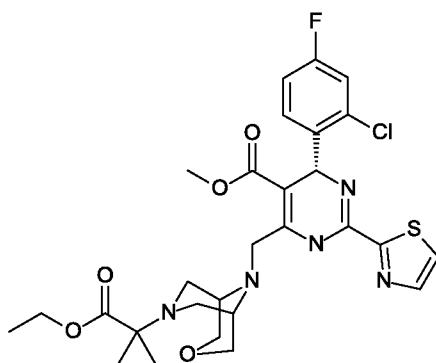
To a solution of chlorosulfonyl isocyanate (0.087 mL, 1 mmol) in CH_2Cl_2 (20 mL) was added tert-butanol (0.096 mL, 1 mmol) in ice-bath. The mixture was stirred at room temperature for 2 hours. A solution of N-tert-butoxycarbonylsulfamoyl chloride in CH_2Cl_2 (~0.05 M) was obtained, which was used for next step without further purification.

To a solution of (R)-4-(2-chloro-4-fluoro-phenyl)-6-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (60 mg, 0.12 mmol) and triethylamine (0.05 mL, 0.36 mmol) in CH_2Cl_2 (10 mL) was added N-tert-butoxycarbonylsulfamoyl chloride in dichloromethane (0.05 M, 2.5 mL, 0.125 mmol) dropwise in ice-bath. The mixture was stirred at 0°C for 1 hour. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography to afford compound **AD** as a brown solid (80 mg, 99%). MS: calc'd (MH^+) 671, measured (MH^+) 671.

Example 20:

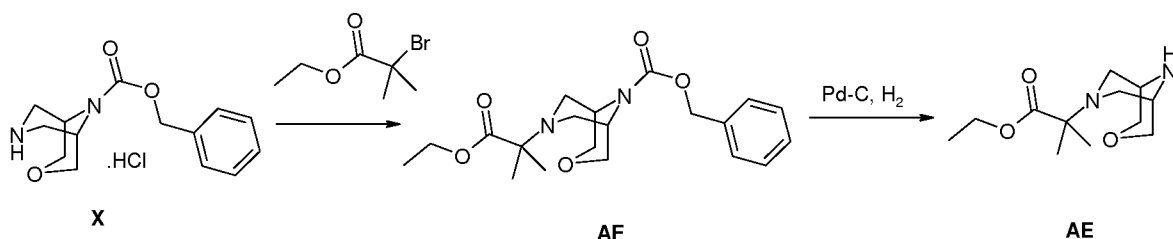
(R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(1-ethoxycarbonyl-1-methyl-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

-124-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 2-methyl-2-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-7-yl)-propionic acid ethyl ester (Compound **AE**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of 2-methyl-2-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-7-yl)-propionic acid ethyl ester (Compound **AE):**

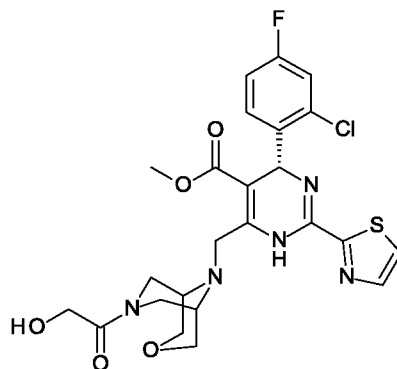


A mixture of 7-(1-ethoxycarbonyl-1-methyl-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound **X**) (130 mg, 0.50 mmol), cesium carbonate (489 mg, 1.5 mmol) and 2-bromo-2-methyl-propionic acid ethyl ester (0.15 mL, 1.0 mmol) in N,N-dimethylformamide (3 mL) was stirred at 80 °C for 5 hours. The mixture was then filtered and washed with ethyl acetate (20 mL × 2). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography to afford 7-(1-ethoxycarbonyl-1-methyl-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound **AF**) as brown oil (0.090 g, 47%). MS: calc'd (MH⁺) 377, measured (MH⁺) 377.

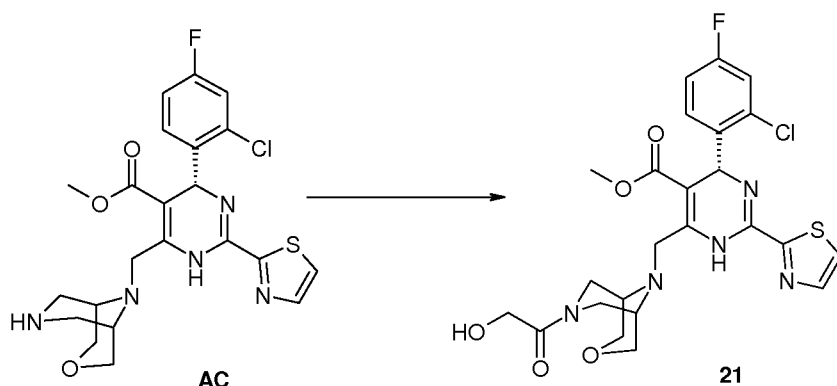
A mixture of 2-methyl-2-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-7-yl)-propionic acid ethyl ester (Compound **AF**) (90 mg, 0.24 mmol) and 10% palladium on activated carbon (20 mg) in methanol (20 mL) was stirred at room temperature under hydrogen pressure (30 psi) for 16 hours. The catalyst was filtered off and the filtrate was concentrate in vacuo to afford 2-methyl-2-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-7-yl)-propionic acid ethyl ester (Compound **AE**) as light yellow oil (55mg, 95%) which was used directly in the coupling reaction without further purification. MS: calc'd (MH⁺) 242, measured (MH⁺) 242.

Example 21:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(2-hydroxy-acetyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



5

Preparation of Example 21:

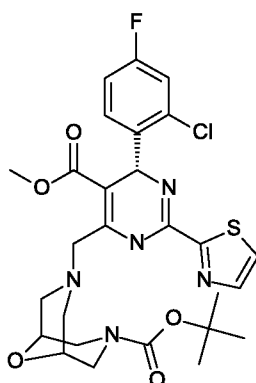
A mixture of (R)-4-(2-chloro-4-fluoro-phenyl)-6-(3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound **AC**) (61.4 mg, 0.125 mmol), glycolic acid (20 mg, 0.25 mmol), EDCI (48 mg, 0.25 mmol) and triethylamine (0.09 mL, 0.625 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo. The residue was purified by preparative HPLC to afford Example **21** as a light yellow solid (10 mg).

15

Example 22:

7-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

-126-

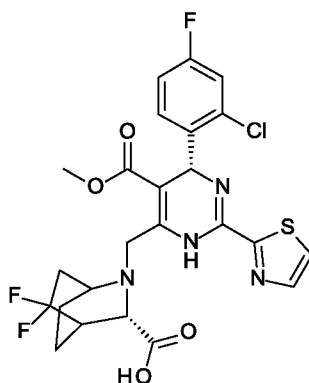


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (WuXi AppTec (Wuhan) Co., Ltd, CAS: 478647-20-0) instead of 3-oxa-9-aza-

5 bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Example 23:

(S)-2-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-5,5-difluoro-2-aza-bicyclo[2.2.2]octane-3-carboxylic acid



10

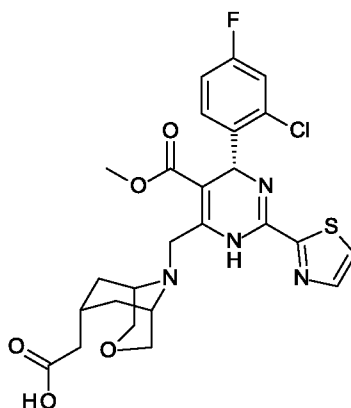
The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using (S)-6,6-difluoro-2-aza-bicyclo[2.2.2]octane-3-carboxylic acid (WuXi AppTec (Wuhan) Co., Ltd, CAS: 1394117-03-3) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

15

Example 24:

(R)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

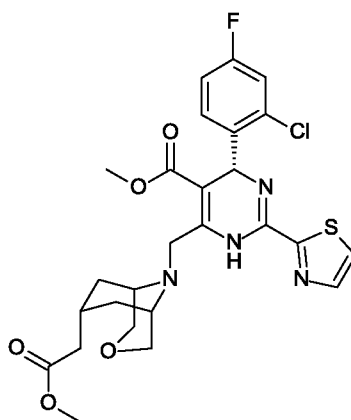
-127-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd, CAS: 1389441-75-1) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Example 25:

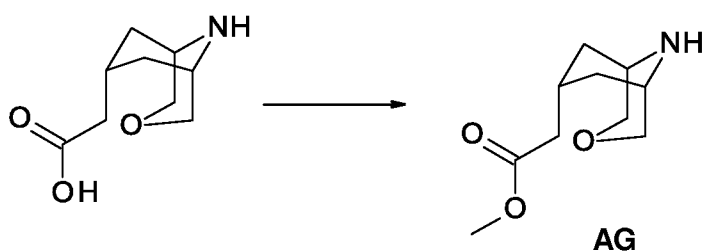
(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methoxycarbonylmethyl-3-oxa-9-azabicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid methyl ester (compound **AG**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of compound **AG**:

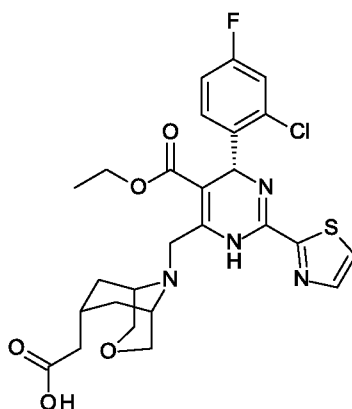
-128-



To a solution of (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (200 mg, 0.9 mmol) in 10 mL of methanol was added dropwise sulfuryl chloride (0.3 mL, 1.8 mmol) under ice cooling. After the mixture was refluxed for 3 hours, it was concentrated in vacuo. The residue was extracted with ethyl acetate (20 mL $\times$ 2). The organic layer was washed with saturated aqueous sodium bicarbonate solution (20 mL $\times$ 2), and then dried over anhydrous sodium sulfate and then concentrated in vacuo to afford (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid methyl ester (Compound **AG**) as colorless oil (179 mg, 99%) which was used directly in next step without further purification. MS: calc'd (MH^+) 200, measured (MH^+) 200.

Example 26:

(R)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid ethyl ester

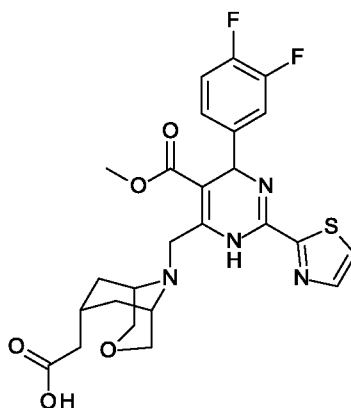


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate instead of methyl acetoacetate and (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd, CAS: 1389441-75-1) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Example 27:

6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(3,4-difluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

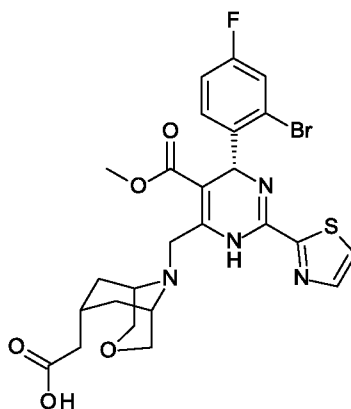
-129-



The title compound was prepared in analogy to Example 3 with the procedure shown in Scheme 4 by using (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd, CAS: 1389441-75-1) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Example 28:

(R)-4-(2-Bromo-4-fluoro-phenyl)-6-(7-carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

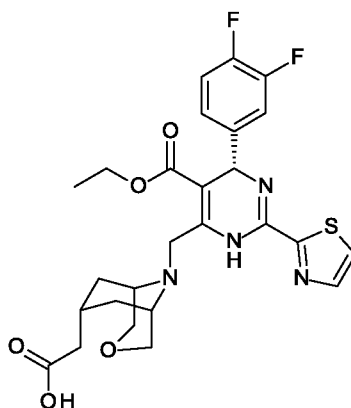


The title compound was prepared in analogy to Example 1a with the procedure shown in Scheme 3 by using 2-bromo-5-fluorobenzaldehyde instead of 2-chloro-5-fluorobenzaldehyde and (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd, CAS: 1389441-75-1) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Example 29

(S)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(3,4-difluorophenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid ethyl ester

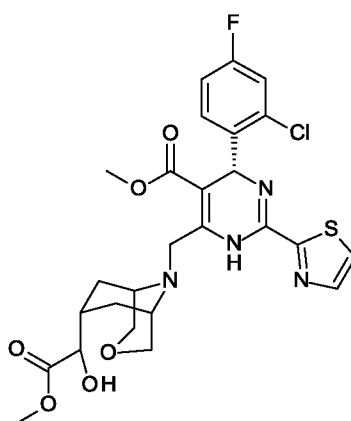
-130-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 3,4-difluorobenzaldehyde instead of 2-chloro-5-fluorobenzaldehyde, ethyl acetoacetate and (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd, CAS: 1389441-75-1) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Example 30:

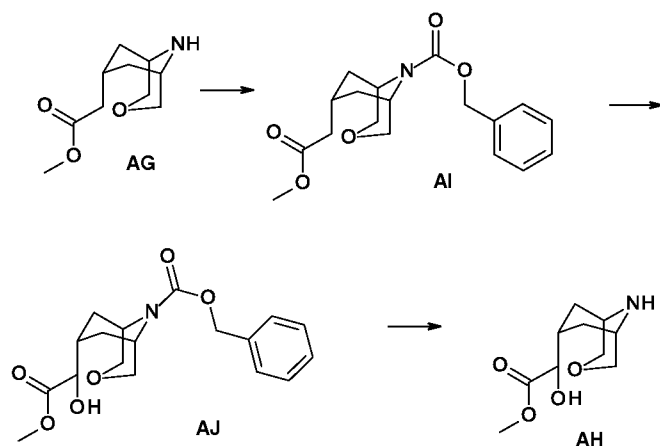
(R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(hydroxy-methoxycarbonyl-methyl)-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using hydroxy-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid methyl ester (Compound **AH**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of hydroxy-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid methyl ester (Compound AH)

-131-



Step I: To a stirred solution of (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid methyl ester (Compound **AG**) (179 mg, 0.90 mmol) in 10 mL of dichloromethane was added triethylamine (0.5 mL, 3.6 mmol). The mixture was stirred at room temperature for 15 mins and then benzyl chloroformate (0.25 mL, 1.8 mmol) was added dropwise at 0 °C. After the reaction mixture was stirred at room temperature for 2 hours, it was concentrated in vacuo. The residue was purified by flash column chromatography to afford 7-methoxycarbonylmethyl-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester as colorless oil (Compound **AI**) (0.13 g, 44%) MS: calc'd (MH⁺) 334, measured (MH⁺) 334.

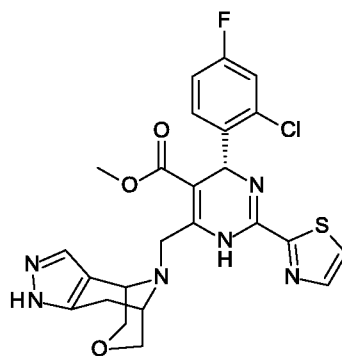
Step II: To a stirred solution of 7-methoxycarbonylmethyl-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound **AI**) (130 mg, 0.39 mmol) in anhydrous THF at -78°C was added 1 M NaN(trimethylsilyl)₂ in THF (0.43mL, 0.43mmol) during a period of 5 mins. Then the mixture was stirred for 20 mins at -78°C. To this solution was added a pre-cooled (-78°C) solution of 2-(phenylsulfonyl)-3-phenyloxaziridine (153 mg, 0.585 mmol) in THF. The solution was stirred for 30 mins at -78°C and then quenched by rapid addition of 6N HCl. The mixture was stirred at room temperature for 30 mins and then diluted with dichloromethane. The mixture was washed with water and 5% aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue was purified by flash column chromatography to afford 7-(hydroxy-methoxycarbonyl-methyl)-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound **AJ**) (0.30 g, 85%). MS: calc'd (MH⁺) 350, measured (MH⁺) 350.

Step III: A mixture of 7-(hydroxy-methoxycarbonyl-methyl)-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-carboxylic acid benzyl ester (Compound **AJ**) (300 mg, 0.86 mmol) and 10% palladium on active carbon (100 mg) in methanol (10 mL) was stirred at room temperature under hydrogen (30 psi) for 16 hours. The catalyst was filtered off. The filtrate was concentrate in vacuo to afford hydroxy-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid methyl ester

(Compound **AH**) (107 mg, 57%) which was used for the next step without further purification.
MS: calc'd (MH⁺) 216, measured (MH⁺) 216.

Example 31:

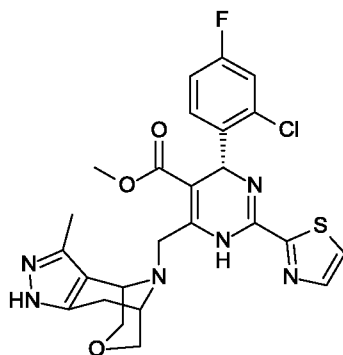
- 5 **(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester**



- 10 The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene-12-carboxylic acid tert-butyl ester (WuXi AppTec (Wuhan) Co., Ltd, CAS: 1311183-41-1) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

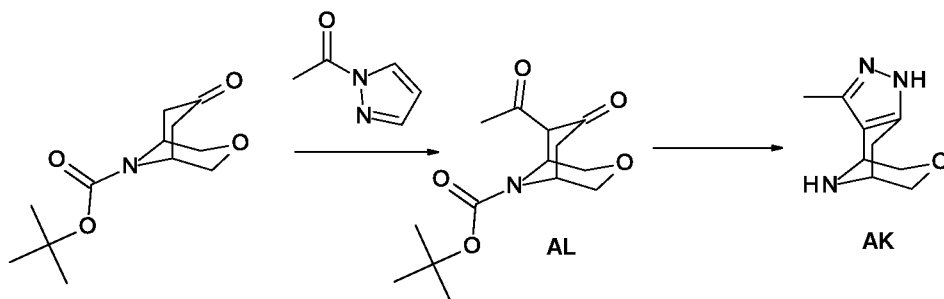
Example 32:

- 15 **(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(3-methyl-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester**



The title compound was prepared in analogy to Example 1a with the procedure shown in Scheme 3 by using 3-methyl-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene (Compound **AK**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of 3-methyl-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene (Compound **AK):**



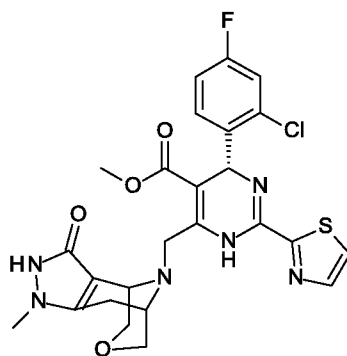
Step I: To a solution of 7-oxo-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-carboxylic acid tert-butyl ester (482 mg, 2 mmol) in THF (5 mL) was added LiHMDS (3 mL, 3 mmol) slowly at -78 °C. After 15 mins, 1-pyrazol-1-yl-ethanone (264 mg, 2.4 mmol) was added, and the resulting mixture was stirred at -78 °C for 1 hour and then at room temperature for 1 hour. The reaction mixture was quenched with water, and then extracted with EA (20 mL × 2). The organic layer was concentrated in vacuo. The residue was purified by flash chromatography (EA in PE 0% ~70%) to afford 6-acetyl-7-oxo-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-carboxylic acid tert-butyl ester (compound **AL**) as light yellow oil (56 mg, 20%). LC/MS: calc'd 284 (MH⁺), exp 284 (MH⁺).

Step II: To a solution of Compound **AL** (56 mg, 0.2 mmol) in EtOH (4 mL) was added hydrazine monohydrate (50 mg, 1.0 mmol), then the reaction mixture was sealed and heated at 80 °C for 2 hours. The reaction mixture was concentrated in vacuo. The residue was dissolved in DCM/TFA (3 mL, 2:1) and then stirred at room temperature for 2 hours. The solvent was removed and the residue was dried under vacuum to afford 3-methyl-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene (Compound **AK**) as yellow foam (crude 50 mg, 100%). LC/MS: calc'd 184 (MH⁺), exp 184 (MH⁺).

Example 33:

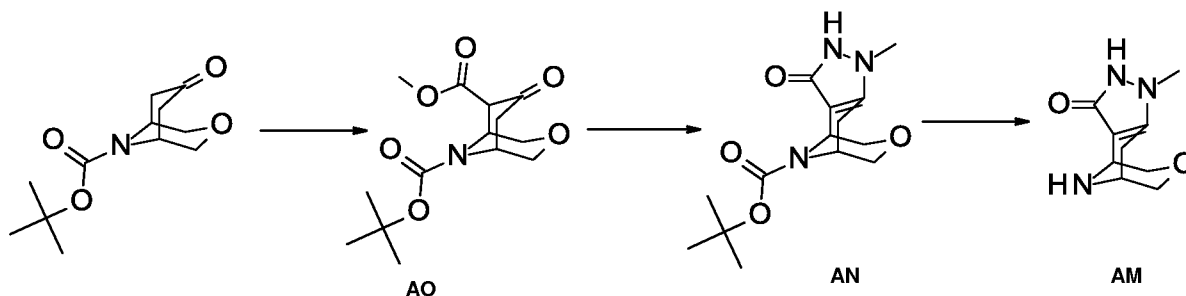
(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(5-methyl-3-oxo-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodec-2(6)-en-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

-134-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 5-methyl-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodec-2(6)-en-3-one (Compound **AM**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

5 Preparation of 5-methyl-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodec-2(6)-en-3-one (Compound AM):



Step I: To a suspension of t-BuOK (1.82 g, 16.26 mmol) in toluene (30 mL) was added dimethyl carbonate (0.98 g, 10.84 mmol). The mixture was heated at 90°C for 5 mins, and then 7-oxo-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-carboxylic acid tert-butyl ester (1.3 g, 5.4 mmol) was added. After the resulting mixture was stirred at 90 °C for 30 mins, the mixture was turned to brown gel, and then DMF (1.5 mL) was added to get a brown solution. The mixture was stirred at 90 °C for 3 hours. After it was cooled to room temperature, silica gel (25 g, 100~200 mesh) was added and the solvent was concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc in PE 0% ~70%) to give 7-oxo-3-oxa-9-aza-bicyclo[3.3.1]nonane-6,9-dicarboxylic acid 9-tert-butyl ester 6-methyl ester (Compound **AO**) as light yellow oil (0.8 g, 49%). LC/MS: calc'd 300 (MH⁺), exp 300 (MH⁺); ¹HNMR(400 MHz, CDCl₃) δ 1.40-1.45 (m, 9H), 2.29-2.41 (m, 1H), 2.68-2.84 (m, 1H), 3.47-3.79 (m, 7H), 3.88-3.96 (m, 0.5 H), 4.09-4.16 (m, 0.3 H), 4.30-4.45 (m, 1H), 4.55-4.67 (m, 0.8 H), 11.86 (s, 0.3 H).

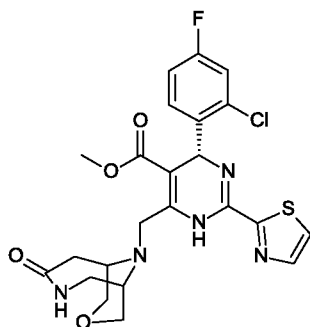
Step II: To a solution of Compound **AO** (250 mg, 0.84 mmol) in EtOH (4 mL) was added 40% methyl hydrazine in water (483 mg, 4.2 mmol). The mixture was sealed and heated at 80°C for 2 hours. The reaction mixture was concentrated in vacuo. The residue was purified by preparative HPLC to afford 5-methyl-3-oxo-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodec-

2(6)-ene-12-carboxylic acid tert-butyl ester (Compound **AN**) as a white solid (99 mg, 40%).
LC/MS: calc'd 296 (MH⁺), exp 296 (MH⁺).

Step III: Compound **AN** (99 mg, 0.33 mmol) was dissolved in DCM/TFA (3 mL, 2:1) and stirred at room temperature for 2 hours. The solvent was removed and the residue was dried under vacuum to afford 5-methyl-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodec-2(6)-en-3-one (Compound **AM**) as a yellow foam (crude 100 mg, 100%). LC/MS: calc'd 196 (MH⁺), exp 196 (MH⁺).

Example 34:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(4-oxo-8-oxa-3,10-diaza-bicyclo[4.3.1]dec-10-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

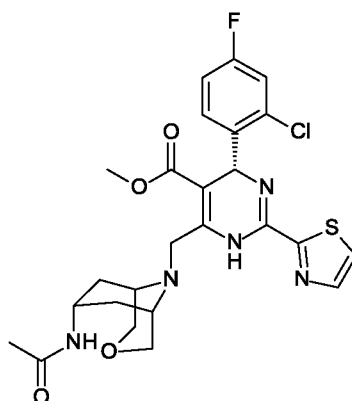


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 4-oxo-8-oxa-3,10-diaza-bicyclo[4.3.1]decane-10-carboxylic acid tert-butyl ester (WuXi AppTec (Wuhan) Co., Ltd, CAS: 1160248-56-5) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Example 35:

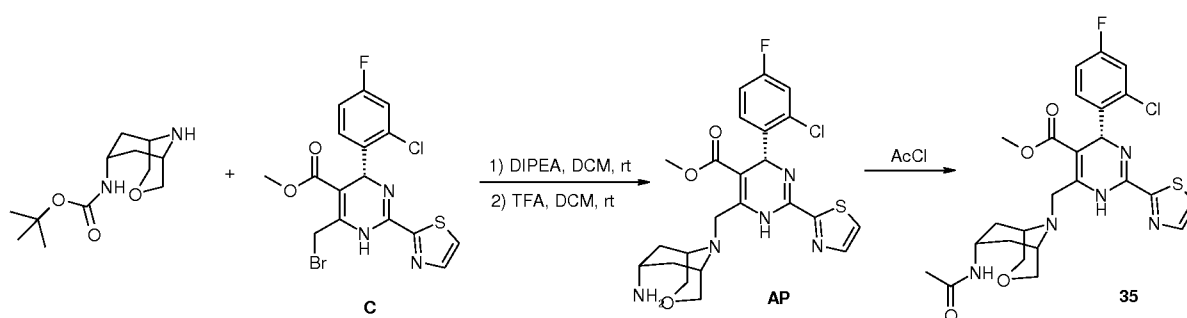
(R)-6-(7-Acetylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

-136-



The title compound was prepared by the procedure shown below (Scheme 6).

Scheme 6



To the solution of (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-carbamic acid tert-butyl ester (PharmaBlock (Nanjing) R&D Co. Ltd, catalog number: PB05636) (106 mg, 0.44 mmol) and Compound **C** (100 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was added DIPEA (0.14 mL, 0.44 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature, then diluted with EtOAc (60 mL). The organic layer was washed with sat. NH_4Cl , sat. NaHCO_3 and brine (20 mL) respectively. The organic layer was dried over Na_2SO_4 , and then concentrated under reduced pressure to give the crude product which was dissolved in CH_2Cl_2 (5 mL). To the solution was added trifluoroacetic acid (2 mL) at 0°C . The mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure to give the crude (R)-6-(7-amino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Compound **AP**) which was directly used for next step.

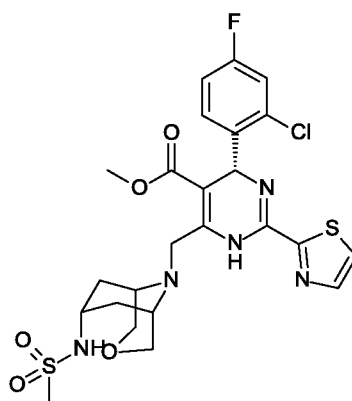
To a solution of Compound **AP** and DIPEA (0.19 mL, 1.10 mmol) in CH_2Cl_2 (5 mL) was added acetyl chloride (31 μL , 0.44 mmol) at 0°C . The reaction mixture was stirred at room temperature for 2 hours, and then quenched with sat. NH_4Cl , then diluted with EtOAc (60 mL). The organic layer was washed with sat. NH_4Cl , sat. NaHCO_3 and brine respectively. The organic

layer was dried over Na₂SO₄, and then concentrated, then purified by reverse phase HPLC to give (R)-6-(7-acetylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester (Example 35) (36 mg) as a light yellow powder.

5

Example 36:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methanesulfonylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

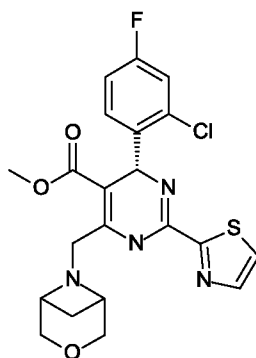


10

The title compound was prepared in analogy to Example 35 with the procedure shown in Scheme 6 by using methanesulfonyl chloride instead of acetyl chloride.

Example 37:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(2-methoxymethyl-azetidin-1-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

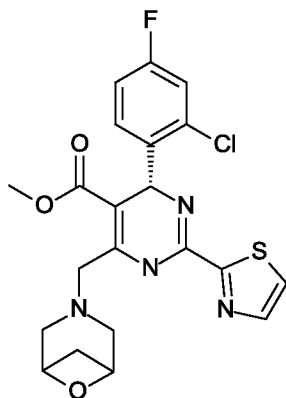


The title compound was prepared in analogy to Example 1a with the procedure shown in Scheme 3 by using 3-oxa-6-azabicyclo[3.1.1]heptane (WuXi AppTec (Wuhan) Co., Ltd, CAS: 286390-20-3) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

20

Example 38:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(6-oxa-3-aza-bicyclo[3.1.1]hept-3-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



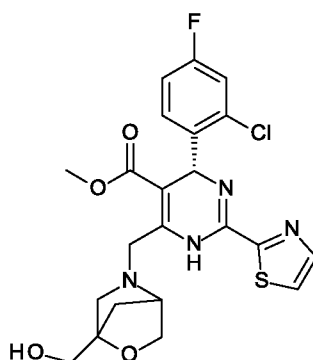
5

The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 6-oxa-3-aza-bicyclo[3.1.1]heptane instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

10

Example 39:

(S)-3-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3,6-diaza-bicyclo[3.2.1]octane-7-carboxylic acid

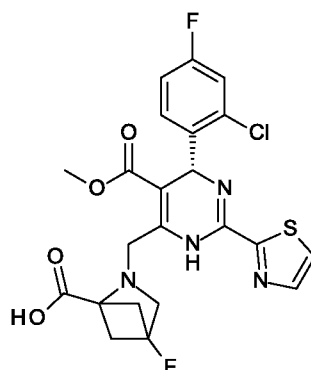


15

The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using (2-oxa-5-aza-bicyclo[2.2.1]hept-1-yl)-methanol (the corresponding Boc protected precursor was purchased from WuXi AppTec (Wuhan) Co., Ltd, CAS: 1357351-86-0) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

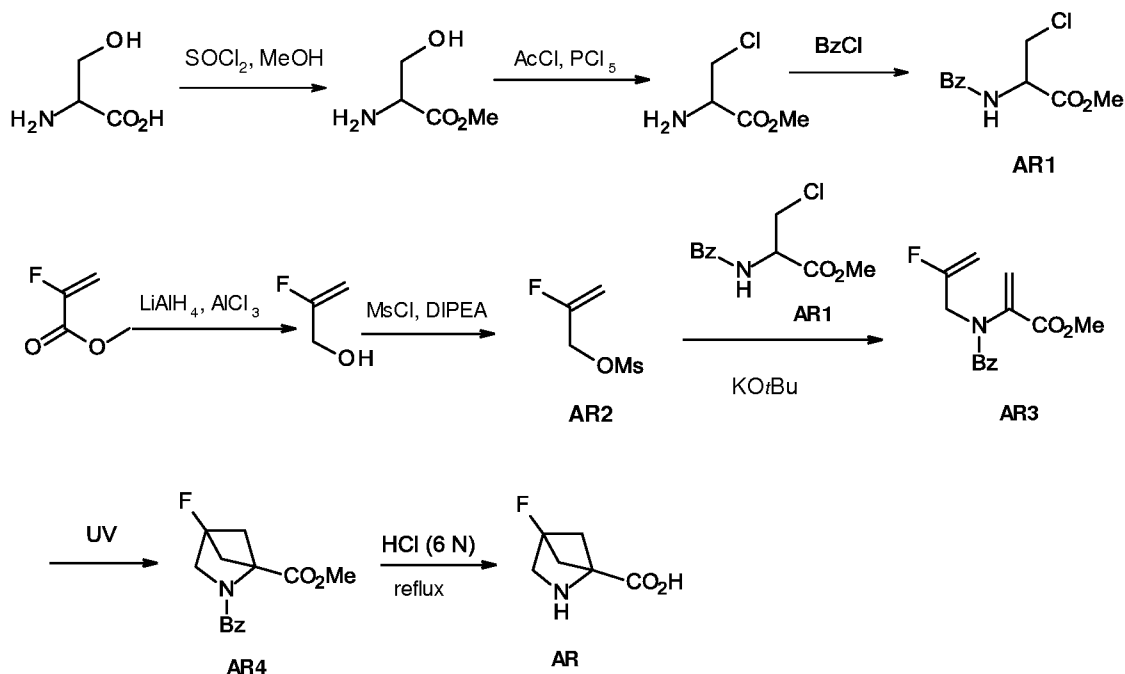
Example 40:

2-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-4-fluoro-2-aza-bicyclo[2.1.1]hexane-1-carboxylic acid



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 4-fluoro-2-aza-bicyclo[2.1.1]hexane-1-carboxylic acid instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of literature known 4-fluoro-2-aza-bicyclo[2.1.1]hexane-1-carboxylic acid (AR):



Step I: To a solution of serine (10.5 g, 100 mmol) in MeOH (100 mL) at 0 °C was added thionyl chloride (8.3 g, 5.1 mL, 70 mmol) over 5 minutes. After the reaction mixture was allowed to warm to room temperature and stirred for 48 hours, it was concentrated to a solid through repetitive evaporation with MeOH (3 x 20 mL), toluene (1 x 20 mL), and hexane (20 mL). The crude white solid was dissolved in acetyl chloride (120 mL), chilled to 0 °C, and phosphorus pentachloride (22.5 g, 107 mmol) was added. The reaction mixture was allowed to

warm to room temperature and was stirred for an additional 9 hours. Then the reaction mixture was cooled, and the solid precipitate was filtered and collected to yield 13.5 g of a light-yellow solid. This solid was suspended in THF (100 mL) and water (5 mL) at 0 °C and reacted with potassium carbonate (27 g, 195 mmol) and benzoyl chloride (26.6 g, 22 mL, 190 mmol) for 1
5 hour at 0 °C. The reaction was stirred for 4 hours at room temperature, then diluted with water (600 mL) and chilled to 0 °C overnight. The solid formed in this reaction mixture was filtered off and dried to yield methyl 2-benzamido-3-chloro-propanoate (**AR1**) (11 g, 42%). LC/MS: calc'd 242 (MH⁺), exp 242 (MH⁺).

Step II: A suspension of LiAlH₄ (6.6 g, 0.17 mol) in Et₂O (150 mL) was treated carefully
10 with AlCl₃ (7.6 g, 0.057 mol) at -5 °C. The resulting mixture was stirred for 30 minutes at -5 °C, and methyl 2-fluoroacrylate (12 g, 0.114 mmol) was added dropwise. The mixture was stirred at -5 °C for additional 1 hour. Thereafter, an excess of wet Na₂SO₄ was added to decompose excess of AlCl₃. Solid phase was separated by filtration and Et₂O was carefully removed at atmospheric pressure to give 7.4 g of 40% solution of 2-fluoroprop-2-en-1-ol in Et₂O which was further
15 diluted with CH₂Cl₂ (20 mL). To this solution, DIPEA (6.33 mL, 0.036 mol) was added. The resulting solution was cooled to -30 °C, and MsCl (2.42 mL, 0.031 mol) was added dropwise. The reaction mixture was allowed to warm to room temperature, and stirred for additional 1 hour. The mixture was washed with water, 10% solution of citric acid, brine, dried over Na₂SO₄, and evaporated under reduced pressure to give 2-fluoroallyl methanesulfonate (**AR2**) (3.77 g, 0.024
20 mol, 93%). The product is relatively unstable and has to be used immediately in the next step.

Step III: A solution of KOtBu (2.35 g, 0.209 mol) in THF (145 mL) was treated under argon at -78 °C with a solution of methyl methyl 2-benzamido-3-chloro-propanoate (**AR1**) (2.35 g, 9.72 mmol) in THF (60 mL), followed by addition of 2-fluoroallyl methanesulfonate (**AR2**) (1.5 g, 9.72 mmol). The reaction mixture was allowed to warm to room temperature, stirred for
25 28 hours, and partitioned between CH₂Cl₂ and H₂O. The organic layer was washed with 10% solution of citric acid, brine, dried over Na₂SO₄, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc = 9/1) to give methyl 2-[benzoyl(2-fluoroallyl)amino]prop-2-enoate (**AR3**) (633 mg, 2.44 mmol, 25%). LC/MS: calc'd 264 (MH⁺), exp 264 (MH⁺).

Step IV: Methyl 2-[benzoyl(2-fluoroallyl)amino]prop-2-enoate (**AR3**) (380 mg, 1.44 mmol), acetophenone (30 mg), benzophenone (40 mg) were dissolved in 25 mL of benzene. The solution formed was irradiated in a quartz reactor by 500W medium pressure mercury lamp at room temperature for 10 hours. The reaction mixture was concentrated, and the residue was

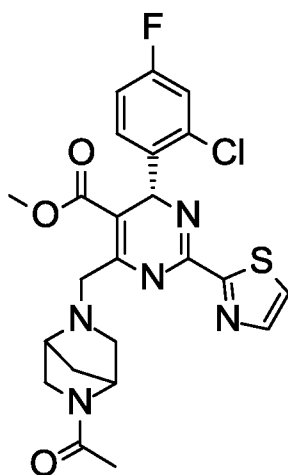
-141-

purified by flash column chromatography (hexane/EtOAc = 3/1) to give methyl 1-fluoro-3-methyl-3-azabicyclo[2.1.1]hexane-4-carboxylate (**AR4**) (240 mg, 0.913 mmol, 63%). LC/MS: calc'd 264 (MH⁺), exp 264 (MH⁺).

Step V: To a solution of methyl 1-fluoro-3-methyl-3-azabicyclo[2.1.1]hexane-4-carboxylate (**AR4**) (150 mg, 0.57 mmol) in CH₂Cl₂ (1.0, mL) was added an aqueous of HCl (6.0 N, 8.0 mL). The reaction mixture was heated to reflux and stirred for 3 hours. After cooled to room temperature, the solution was filtered. The filtrate was evaporated in vacuo, and the residue was washed with MeCN to give 4-fluoro-2-aza-bicyclo[2.1.1]hexane-1-carboxylic acid as a white solid (45 mg). LC/MS: calc'd 146 (MH⁺), exp 146 (MH⁺).

Example 41:

(R)-6-(5-Acetyl-2,5-diaza-bicyclo[2.2.1]hept-2-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

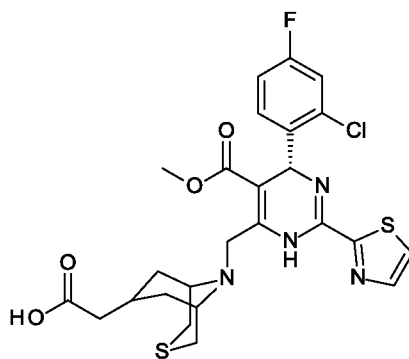


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 1-(2,5-diaza-bicyclo[2.2.1]hept-2-yl)-ethanone instead of 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Example 42:

6-(7-Carboxymethyl-3-thia-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

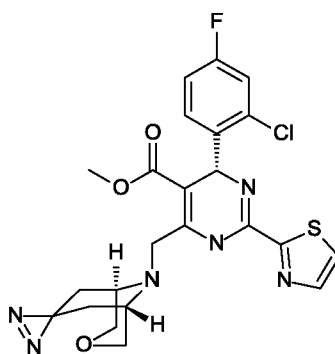
-142-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 3-thia-9-azabicyclo[3.3.1]nonan-7-one hydrochloride (PharmaBlock (Nanjing) R&D Co. Ltd, CAS: 1205682-24-1) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Example 43:

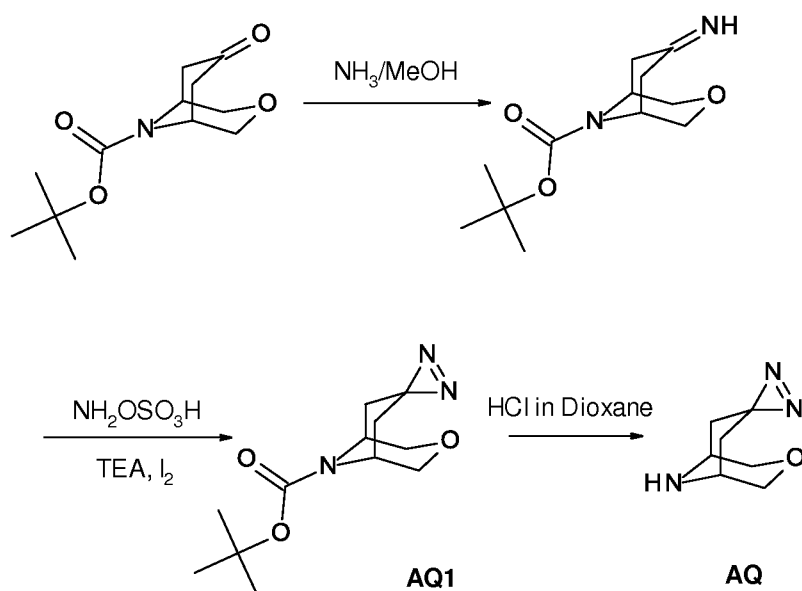
(R)-6-(7-Diazirine-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluorophenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 7-diazirine-3-oxa-9-aza-bicyclo[3.3.1]nonane (Compound **AQ**) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of 7-diazirine-3-oxa-9-aza-bicyclo[3.3.1]nonane (Compound **AQ):**

-143-



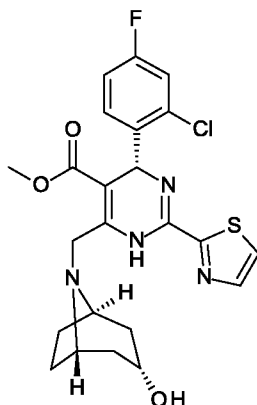
Step I & II: 7-Oxo-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-carboxylic acid tert-butyl ester (200 mg, 0.83 mmol) was added to a solution of NH_3/MeOH (4.0 M, 4 mL). The reaction was heated to 60 °C and stirred for 16 hours. After the solution was cooled to room temperature, 5 $\text{NH}_2\text{OSO}_3\text{H}$ (94 mg, 0.83 mmol) was added. The mixture was stirred at room temperature for 2 hours, and then TEA (84 mg, 0.83 mmol) was added. The solution was cooled to 0 °C, a solution of I_2 (1.0 M) was added until an orange color appeared. The solvent was removed and the residue was dissolved in water (5 mL). The aqueous layer was extracted with EA (10 mL) three times. The combined organic layer was dried over Na_2SO_4 . The solvent was removed to give crude 10 Compound AQ1 as brown oil (180 mg) which was used at next step without further purification. LC/MS: calc'd 254 (MH^+), exp 254 (MH^+).

Step III: To a solution of crude Compound AQ1 (180 mg) in DCM (3.0 mL) was added a solution of HCl/dioxane (4 M, 2.0 mL). After the reaction mixture was stirred at room 15 temperature for 16 hours, the solvent was removed and the residue was dissolved in water (3 mL). The aqueous solution was washed with DCM to remove water insoluble impurity and the water solution was then lyophilized to give 7-diazirine-3-oxa-9-aza-bicyclo[3.3.1]nonane (Compound AQ) as a white solid (80 mg). LC/MS: calc'd 154 (MH^+), exp 154 (MH^+).

Example 44:

20 **(R)-4-(2-Chloro-4-fluoro-phenyl)-6-((1R,3R,5S)-3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester**

-144-

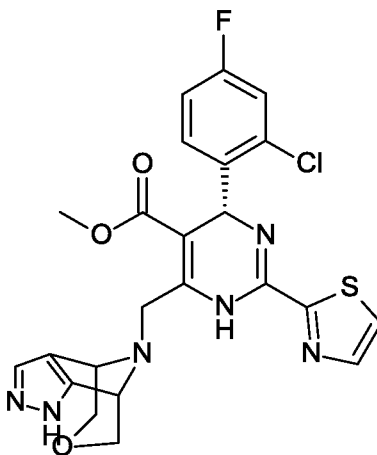


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using (1R,3R,5S)-8-aza-bicyclo[3.2.1]octan-3-ol (BePharm (Shanghai) Ltd, CAS: 14383-51-8) instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

5

Example 45:

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(9-oxa-3,4,11-triaza-tricyclo[5.3.1.0*2,6*]undeca-2(6),4-dien-11-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

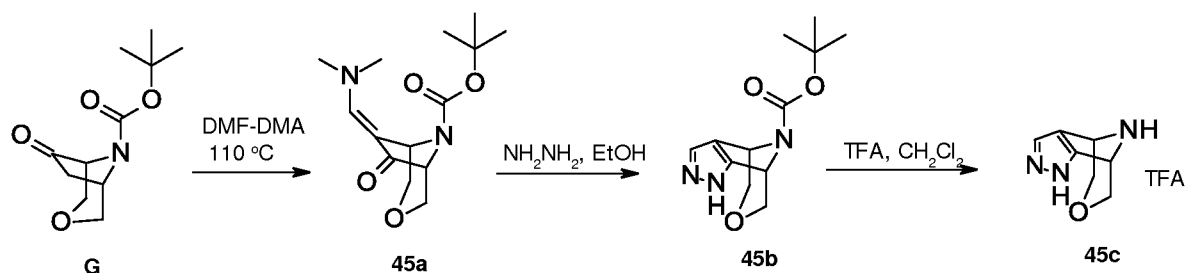


10

The title compound was prepared in analogy to compound **1a** in example **1** starting from compound **C** and compound **45c**.

Preparation of compound 45c

-145-



Step I: A mixture of compound **G** (227mg, 1 mmol) and DMF-DMA (10mL) was heated to reflux at 110 °C for 48 hours. After the starting material disappeared as monitored by LCMS and TLC, the mixture was cooled to room temperature and poured into 50 mL ice-water. The mixture was extracted with ethyl acetate and the combined organic layer was washed with brine and dried over anhydrous Na₂SO₄. The organic solvent was removed to give compound **45a** as crude product, which was directly used for next step without further purification. LC/MS: calc'd 283 (MH⁺), exp 283 (MH⁺).

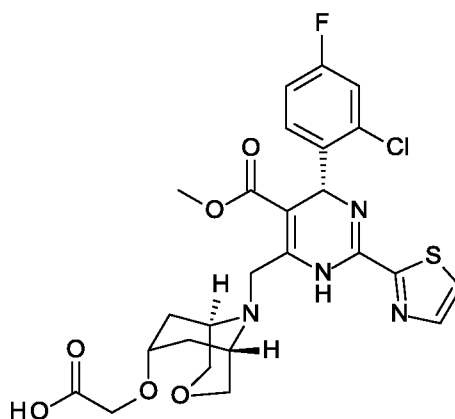
Step II: The crude compound **45a** was dissolved into 15mL of ethanol. To this solution, 0.5 mL hydrazine monohydrate and 3 mL acetic acid were added. The reaction mixture was sealed, heated to 110 °C and stirred overnight. The solvents were removed by reduced pressure and the residue was purified by Prep-HPLC to give white pure product **45b** (32 mg, 13%). MS: calc'd (MH⁺) 252, measured (MH⁺) 252¹H NMR (CDCl₃, 400 MHz): 7.30 (s, 1H), 5.07 (m, 1H), 4.96 (m, 1H), 3.90 (m, 2H), 3.72 (d, J = 10.8 Hz, 1H), 3.57 (d, J = 10.8 Hz, 1H), 1.49 (s, 9H) ppm.

Step III: To the solution of compound **45b** (32 mg, 0.13 mmol) in CH₂Cl₂ (4 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred at room temperature for 1h. The solvent was removed under reduced pressure to give the crude product **45c** (35 mg, 100%) which was directly used for next step without further purification. LC/MS: calc'd 152 (MH⁺), exp 152 (MH⁺).

Example 46:

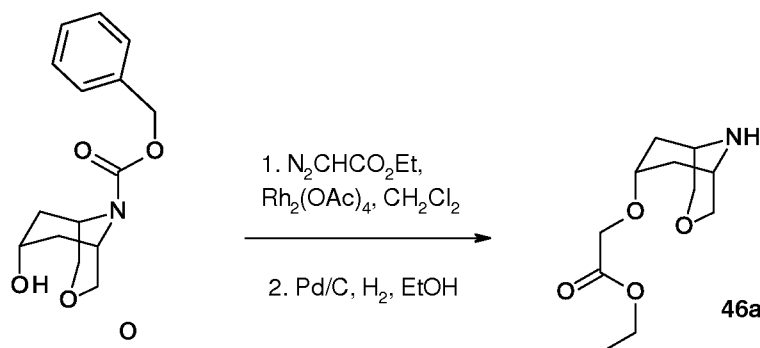
2-[[[(1R,5S)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]oxy]acetic acid

-146-



The title compound was prepared in analogy to Example 1 with the procedure shown in Scheme 3 by using ethyl 2-(3-oxa-9-azabicyclo[3.3.1]nonan-7-yloxy)acetate **46a** instead of 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

5 Preparation of ethyl 2-(3-oxa-9-azabicyclo[3.3.1]nonan-7-yloxy)acetate **46a**



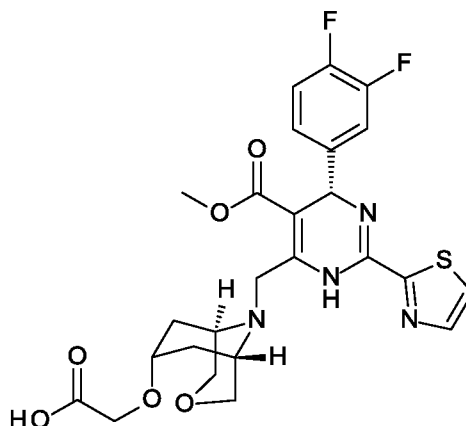
Step I: To a solution of benzyl 7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **O** (200 mg, 0.72 mmol) in DCM (4 mL) was added ethyl 2-diazoacetate (202 mg, 1.44 mmol) and Rhodium(II) acetate (319 mg, 0.72 mmol) at 0 °C. The resulting mixture was stirred at room temperature for overnight, and then diluted with EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried (Na₂SO₄). The organic solvent was removed in vacuo to give the crude product, which was purified by column chromatography to give the intermediate benzyl 7-(2-ethoxy-2-oxo-ethoxy)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (144 mg, 55%). LC/MS: calc'd 364 (MH⁺), exp 364 (MH⁺).

Step II: To a solution of intermediate benzyl 7-(2-ethoxy-2-oxo-ethoxy)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (144 mg, 0.40 mmol) in EtOH (10 mL) was added 10% Pd/C (20 mg). The mixture was charged with H₂ and being stirred at room temperature for 2 h. The mixture was filtered through a pad of Celite and washed with EtOH. The resulting filtrate was concentrated in vacuo to give compound **46a** (83 mg, 91%). LC/MS: calc'd 230 (MH⁺), exp

230 (MH⁺); ¹H NMR (MeOD, 400 MHz): 4.18 (dd, J = 14.0, 6.8 Hz, 2H), 4.13 (s, 2H), 3.74 (m, 1H), 3.68 (m, 4H), 2.98 (m, 2H), 2.27 (m, 2H), 1.77 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H).

Example 47:

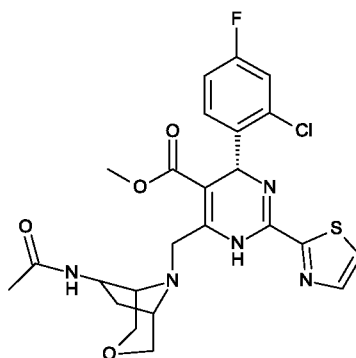
5 2-[[[(1R,5S)-9-[[[(4S)-4-(3,4-difluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]oxy]acetic acid



The title compound was prepared in analogy to Example 1 with the procedure shown in Scheme 3 by using 3,4-di-fluoro-benzaldehyde and ethyl 2-(3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)oxyacetate instead of 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

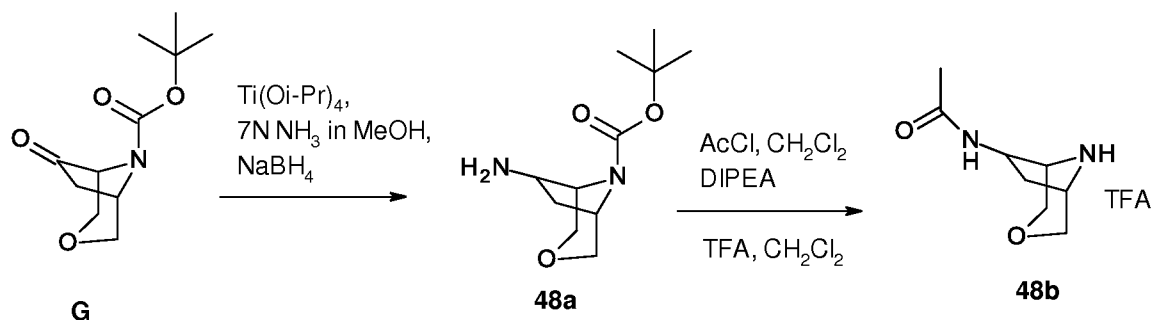
Example 48:

15 Methyl (4R)-6-[(6-acetamido-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate



The title compound was prepared in analogy to Example 1 with the procedure shown in Scheme 3 by using N-(3-oxa-8-azabicyclo[3.2.1]octan-6-yl)acetamide (48b) instead of 3-oxa-9-

azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester. **Preparation of N-(3-oxa-8-azabicyclo[3.2.1]octan-6-yl)acetamide 48b**



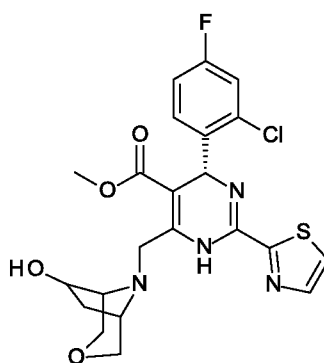
- 5 **Step I:** A mixture of compound **G** (100 mg, 0.44 mmol), titanium(IV) isopropylate (250 mg, 0.88 mmol) and ammonia in CH₃OH(20 ml, 7N) was stirred under N₂ in a capped flask at room temperature for 6h. Then NaBH₄ (50 mg, 1.32 mmol) was added to the mixture and stirred at room temperature for 3h. The reaction was then quenched by pouring it into NH₃.H₂O(2M , 20 ml) and extracted with EA. The organic layer was dried over Na₂SO₄ and concentrated. The
- 10 resulting residue was purified by pre-HPLC to give the product **48a** (30 mg, 30%) as white solid. LC/MS: calc'd 229 (MH⁺), exp 229 (MH⁺). ¹HNMR (400 MHz, CDCl₃): 1.48-1.64 (m, 12H), 2.51-2.58 (m, 1H), 3.56-3.63 (m, 2H), 3.72-3.89 (m, 3H), 4.04-4.13 (m, 2H).

- 15 **Step II:** To the solution of compound **48a** (30 mg, 0.13 mmol) and i-PrNEt₂ (0.22 mL, 1.3 mmol) in CH₂Cl₂ (5 mL) at 0 °C was added AcCl (46 μL, 0.65 mmol). The mixture was stirred
- 20 at room temperature for 1h, quenched with Sat. NH₄Cl, diluted with EtOAc (50 mL). The organic layer was separated, washed with sat. NH₄Cl, sat. NaHCO₃ and brine, dried over Na₂SO₄ and concentrated to give a crude residue (30 mg, 86%), which was treated with 30% TFA in DCM. The mixture was stirred at room temperature for 1h, solvent was evaporated to give a crude product **48b** (30 mg, 95%) which was directly used for next step. LC/MS: calc'd 171 (MH⁺), exp 171 (MH⁺).

Example 49:

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-hydroxy-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate

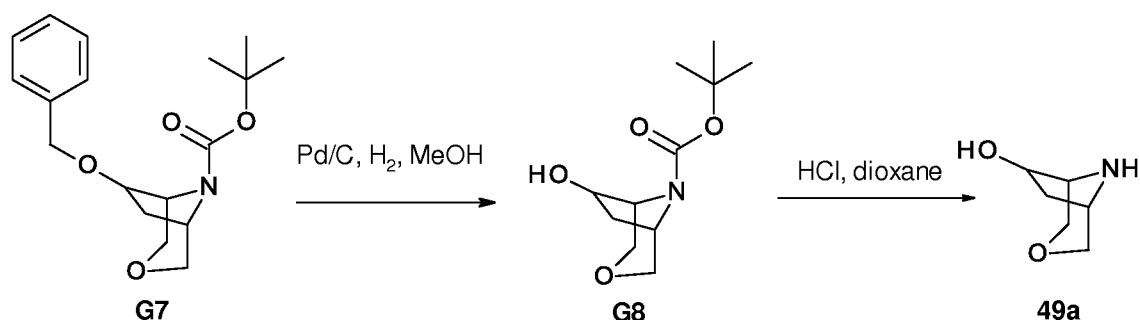
-149-



The title compound was prepared in analogy to compound **1a** in Example 1 by using compound **49a** instead of 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester.

Preparation of 3-oxa-8-azabicyclo[3.2.1]octan-6-ol (**49a**)

5



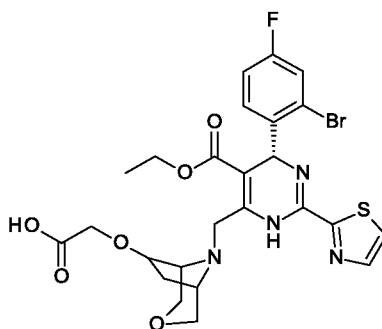
Step I: A mixture of (1R,5R,6R)-tert-butyl 6-(benzyloxy)-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate **G7** (racemic, 800mg, 2.51 mmol), 10% Pd/C (300 mg) and MeOH (20 mL) was hydrogenated under 50 psi at 40 °C for 24 h. The mixture was filtered through a pad of Celite and washed with MeOH. The resulting filtrate was concentrated in vacuo to give compound **G8** (520mg, 91%). LC/MS: calc'd 252 (MH⁺), exp 252 (MH⁺); ¹H NMR (METHANOL-d₄, 400 MHz): 4.39 (m, 1H), 4.13 (m, 1H), 3.75 (m, 1H), 3.60 (d, J = 11.2 Hz, 1H), 3.43 (m, 2H), 3.20 (m, 1H), 2.23 (m, 1H), 1.68 (m, 1H), 1.39 (s, 9H).

Step II: Compound **G8** (100 mg, 0.44 mmol) was dissolved in 4M HCl in Dioxane (5 mL). The solution was being stirred at room temperature for 1 h, then the solvent was evaporated under reduced pressure to give compound **49a** (70 mg, 95%) as white solid. LC/MS: calc'd 130 (MH⁺), exp 130 (MH⁺).

Example 50:

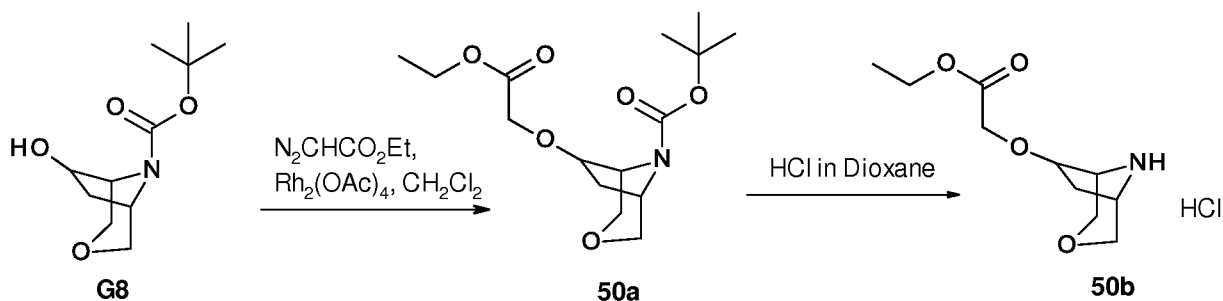
2-[[8-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]oxy]acetic acid

-150-



The title compound was prepared in analogy to Example 1 with the procedure shown in Scheme 3 by using ethyl 3-oxobutanoate, 2-bromo-4-fluoro-benzaldehyde and ethyl 2-(3-oxa-8-azabicyclo[3.2.1]octan-6-yloxy)acetate **50b** instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Preparation of ethyl 2-(3-oxa-8-azabicyclo[3.2.1]octan-6-yloxy)acetate (**50b**)



Step I: To a solution of tert-butyl 6-hydroxy-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate **G8** (racemic, 200 mg, 0.87 mmol) in DCM (4 mL) was added ethyl 2-diazoacetate (246 mg, 1.75 mmol) and Rhodium(II) acetate (386 mg, 0.87 mmol) at 0 °C. The resulting mixture was stirred at room temperature for overnight, and then diluted with EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried (Na₂SO₄). The organic solvent was removed in vacuo to give the crude product, which was purified by column chromatography on silica gel with EtOAc/PE (50:100) to give the compound **50a** (205 mg, 75%). LC/MS: calc'd 216 (M-Boc+H⁺), exp 216 (M-Boc+H⁺).

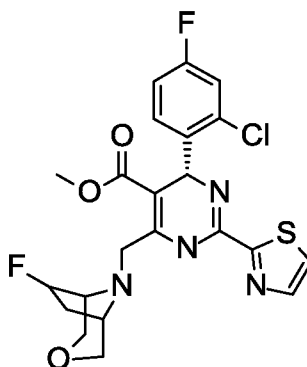
Step II: To a solution of (1R,5R,6R)-tert-butyl 6-(2-ethoxy-2-oxoethoxy)-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate **50a** (racemic, 200 mg, 0.63 mmol) in DCM (10 mL) was added HCl/dioxane (2 mL, 7 M). The resulting mixture was stirred at room temperature for 2 h. The organic solvent was removed in vacuo to give the compound **50b** (150 mg, 94%). MS:

-151-

calc'd (MH⁺) 216, measured (MH⁺) 216; ¹H NMR (CDCl₃, 400 MHz): 4.28 (m, 8H), 3.79(m, 1H), 3.70(s, 1H), 3.57(d, J = 12.4 Hz, 1H), 2.50(m, 1H), 2.31(m, 1H), 1.28(m, 3H).

Example 51:

- 5 **Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-fluoro-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate**

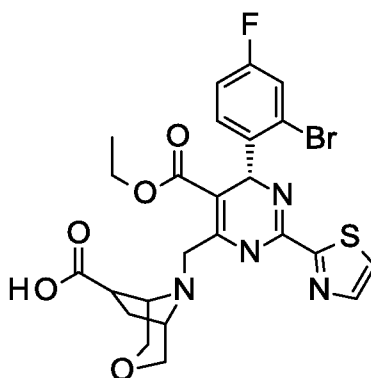


- The title compound was prepared in analogy to compound **1a** in Example 1 starting from compound **C** and compound 6-fluoro-3-oxa-8-azabicyclo[3.2.1]octane **51a**. **Preparation of 6-fluoro-3-oxa-8-azabicyclo[3.2.1]octane 51a:**

Compound **51a** was prepared from tert-butyl 6-hydroxy-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate **G8** by treatment with DAST (diethylaminosulfur trifluoride) followed by HCl/dioxane to remove the N-Boc protection.

- 15 **Example 52:**

8-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-6-carboxylic acid

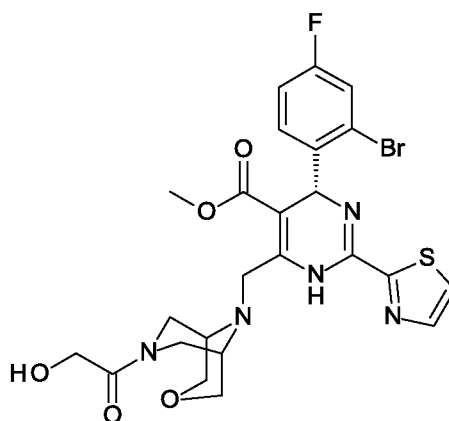


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl 3-oxobutanoate, 2-bromo-4-fluoro-benzaldehyde and 3-oxa-8-azabicyclo[3.2.1]octane-6-carboxylic acid **F** instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

5

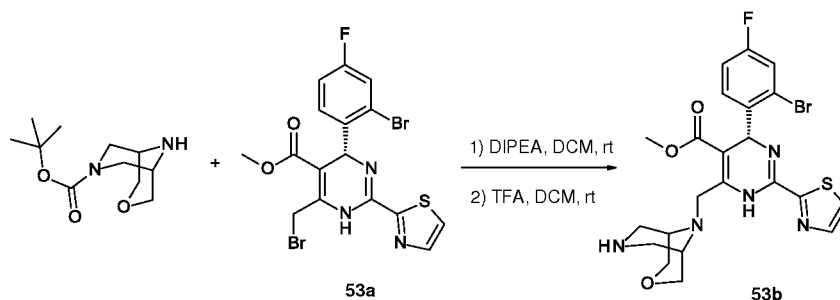
Example 53:

Methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-[[7-(2-hydroxyacetyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate



The title compound was prepared in analogy to Example **21** by using methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **53b** instead of Compound **AC**. **53b** (67 mg, 0.125 mmol) and glycolic acid (20 mg, 0.25 mmol) afforded 14 mg of Example **53**.

Preparation of methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **53b**

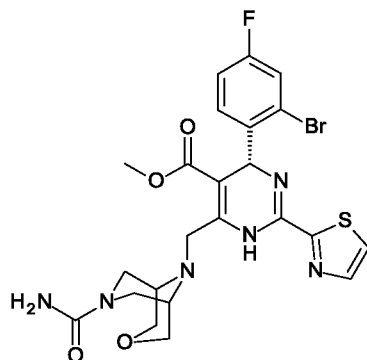


Compound **53b** was prepared in analogy to intermediate **AC** in Example **15**, starting from 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester and methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **53a**, while **53a** was prepared in analogy to compound **C** in Example **1**.

20

Example 54:

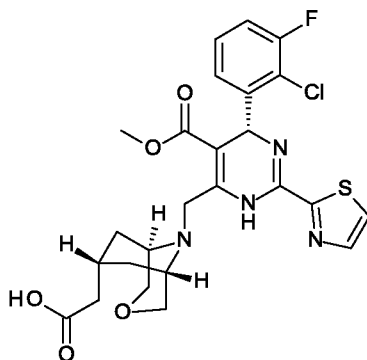
Methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-[(7-carbamoyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate



The title compound was prepared in analogy to Example **18** starting from methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **53b** (50 mg, 0.09mmol) and isocyanato(trimethyl)silane (43 mg, 0.37 mmol). 37 mg of the title compound was isolated as a light yellow powder.

Example 55:

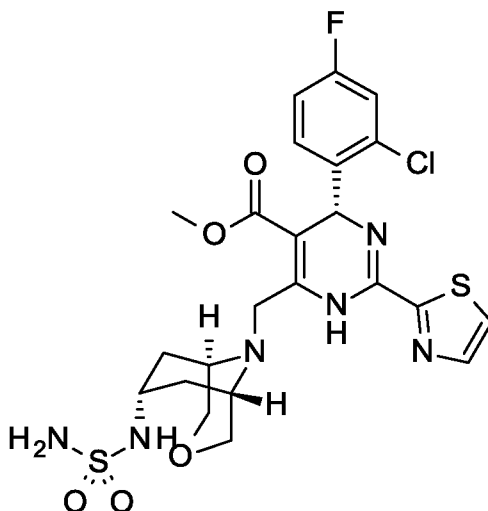
2-[(1R,5S)-9-[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid



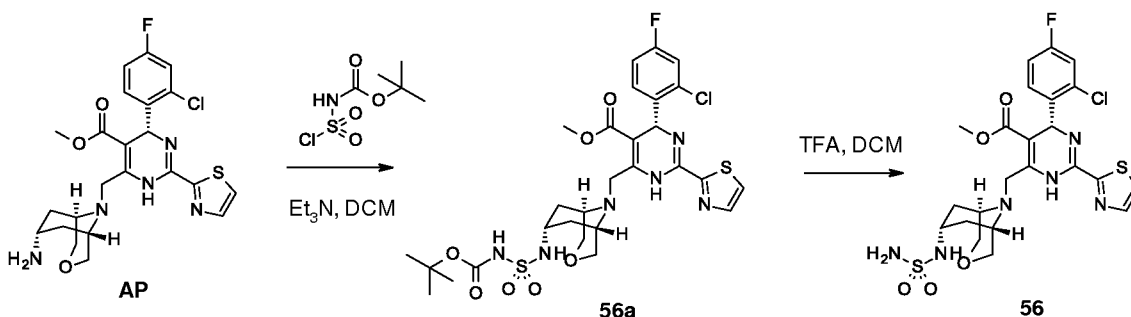
The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 2-chloro-3-fluoro-benzaldehyde and (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PBN20121752 , CAS: 1389441-75-1) instead of 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 56:

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[[(1R,5S)-7-endo-(sulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate



5 Preparation of Example 56:



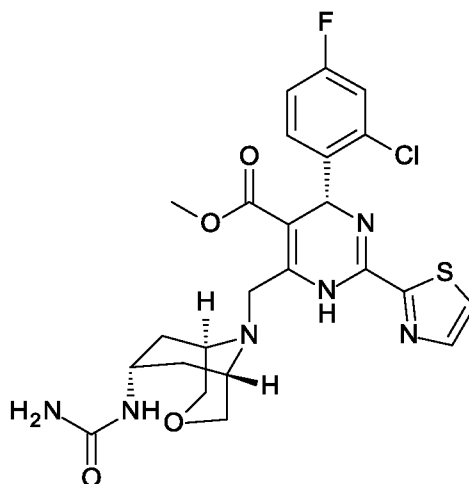
Step I: To a solution of methyl (4R)-6-[[[(1S,5R)-7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **AP** (60 mg, 0.12 mmol) and triethyl-amine (0.05 mL, 0.36 mmol) in DCM (5 mL) was added a 0.05 M solution of tert-butyl N-chlorosulfonfylcarbamate in DCM (2.5 mL, 0.125 mmol) dropwise at 0 °C. The mixture was allowed to warm to room temperature while stirred for 16 h. Then the mixture was concentrated in vacuo. The residue was purified by flash silica gel chromatography to afford 0.08 g of the product **56a** as a yellow oil (yield was 97%). MS: calc'd (MH⁺) 684, measured (MH⁺) 684.

Step II: To a solution of methyl (4R)-6-[[[(1S,5R)-7-(tert-butoxycarbonylsulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **56a** (80 mg, 0.12 mmol) in DCM (5 mL) was added TFA (0.5 mL). The mixture was stirred at 25 °C for 3 h. The mixture was concentrated in vacuo. The

residue was purified by Preparative HPLC to afford 30 mg of the Example **56** as a light yellow powder (yield was 42%).

Example 57:

5 **Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-6-[(1S,5R)-7-endo-ureido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-1,4-dihydropyrimidine-5-carboxylate**



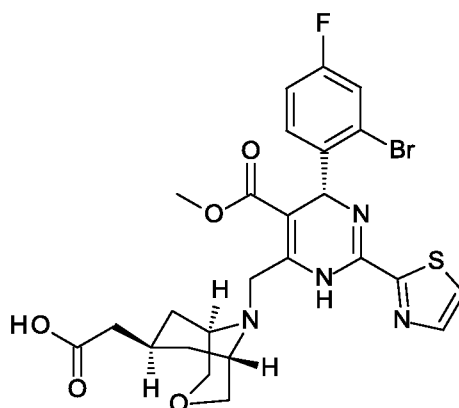
To a solution of methyl (4R)-6-[(1S,5R)-7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **AP** (60 mg, 0.12mmol) and triethyl-amine (0.17 mL, 1.2 mmol) in DCM (5 mL) was added isocyanato(trimethyl)silane (55 mg, 0.48 mmol) dropwise at 0 °C. The mixture was allowed to warm to room temperature while stirred for 16 h. Then the mixture was concentrated in vacuo. The residue was purified by preparative HPLC to afford 30 mg of the Example **57** as a light yellow powder (yield was 45%).

15

Example 58:

2-[(1S,5R)-9-[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

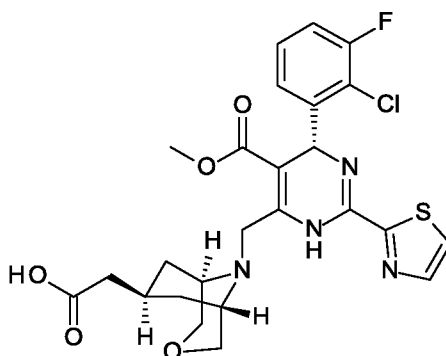
-156-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 2-bromo-4-fluoro-benzaldehyde and exo-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 59:

Exo-2-[(1S,5R)-9-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

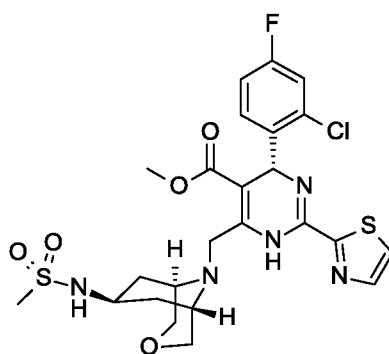


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 2-chloro-3-fluoro-benzaldehyde and exo-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

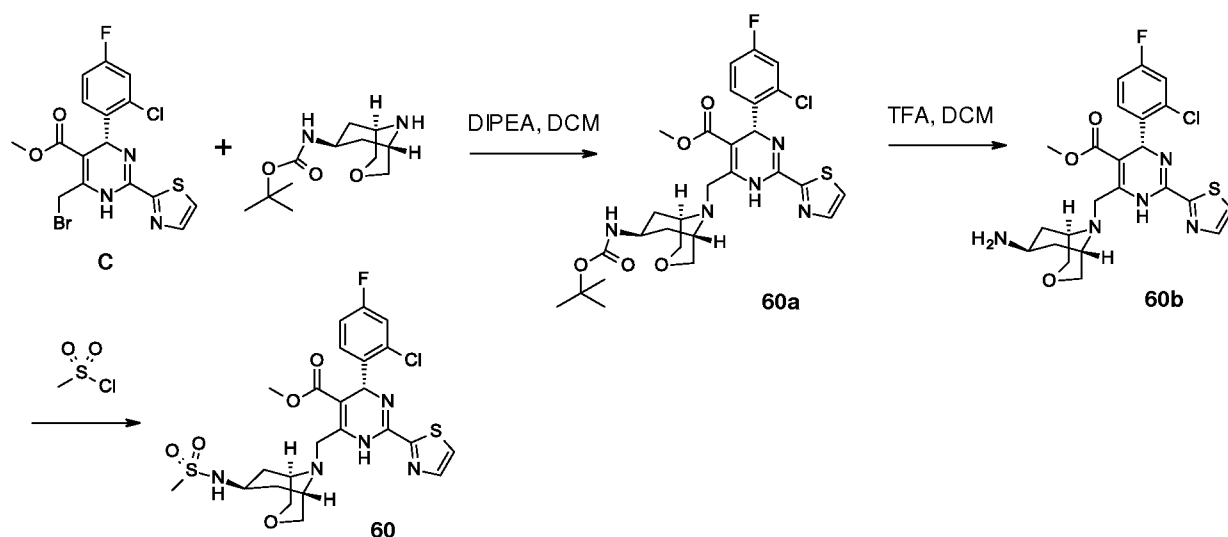
Example 60:

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[(1R,5S)-7-exo-(methanesulfonamido)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate

-157-



Preparation of Example 60



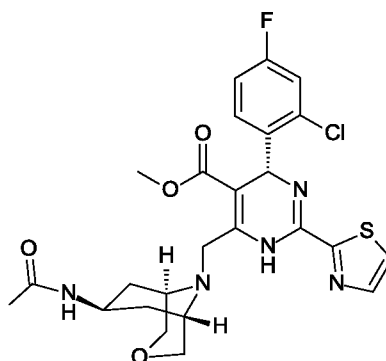
5 **Step I:** A mixture of methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (222 mg, 0.5 mmol, compound C, tert-butyl exo-N-[(1R,5S)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]carbamate (158 mg, 0.65 mmol) and DIPEA (0.26 mL, 1.5 mmol) in dichloromethane (10 mL). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated in vacuo. The
10 residue was purified by silica gel chromatography to afford 0.3 g of the product **60a** as a yellow oil (yield was 99%). MS: calc'd (MH⁺) 606, measured (MH⁺) 606.

15 **Step II:** To a solution of methyl (4R)-6-[[[(1S,5R)-7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **60a** (300 mg, 0.49 mmol) in DCM (5 mL) was added TFA (2 mL). The mixture was stirred at 25°C for 5 h. The mixture was concentrated in vacuo to afford methyl (4R)-6-[[[(1S,5R)-7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **60b** (240 mg, 96%) which was used for next step without further purification. MS: calc'd (MH⁺) 506, measured (MH⁺) 506.

Step III: To a solution of methyl (4R)-6-[[[(1S,5R)-7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate **60b** (60 mg, 0.12 mmol) and triethyl-amine (0.05 mL, 0.3 mmol) in DCM (5 mL) was added methanesulfonyl chloride (0.018 mL, 0.24 mmol) dropwise at 0°C. The mixture was allowed to warm to room temperature while stirred for 1 h. Then the mixture was concentrated in vacuo. The residue was purified by preparative HPLC to afford 20 mg of the product **60** as a light yellow powder (yield was 28%).

Example 61:

Methyl (4R)-6-[[[(1S,5R)-7-exo-acetamido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate

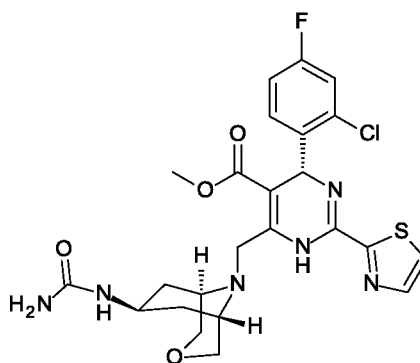


To a solution of methyl (4R)-6-[[[(1S,5R)-7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate **60b** (60 mg, 0.12 mmol) and triethyl-amine (0.05 mL, 0.3 mmol) in DCM (5 mL) was added acetyl chloride (0.018 mL, 0.24 mmol) dropwise at 0°C. The mixture was allowed to warm to room temperature while stirred for 1 h, and then concentrated in vacuo. The residue was purified by preparative HPLC to afford 23 mg of the title compound **61** as a light yellow powder (yield was 34%).

Example 62:

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-6-[[[(1S,5R)-7-exo-ureido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-1,4-dihydropyrimidine-5-carboxylate

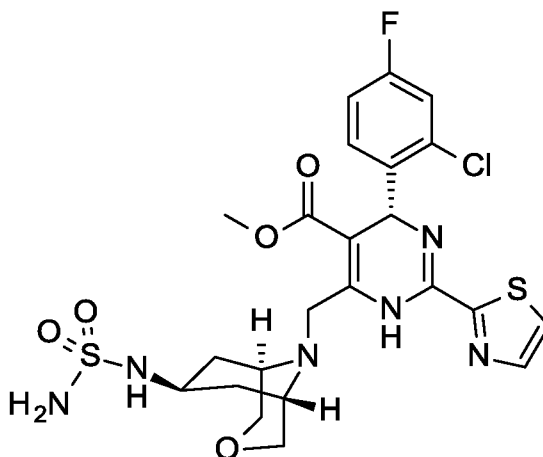
-159-



To a solution of methyl (4R)-6-[[[(1S,5R)-7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate **60b** (60 mg, 0.12mmol) and triethyl-amine (0.17 mL, 1.2 mmol) in DCM (5 mL) was added isocyanato(trimethyl)silane (55 mg, 0.48 mmol) dropwise at 0°C. The mixture was allowed to warm to room temperature while stirred for 3 h. Then the mixture was concentrated in vacuo. The residue was purified by Preparative HPLC to afford 23 mg of the title compound **62** as a light yellow powder (yield was 34%).

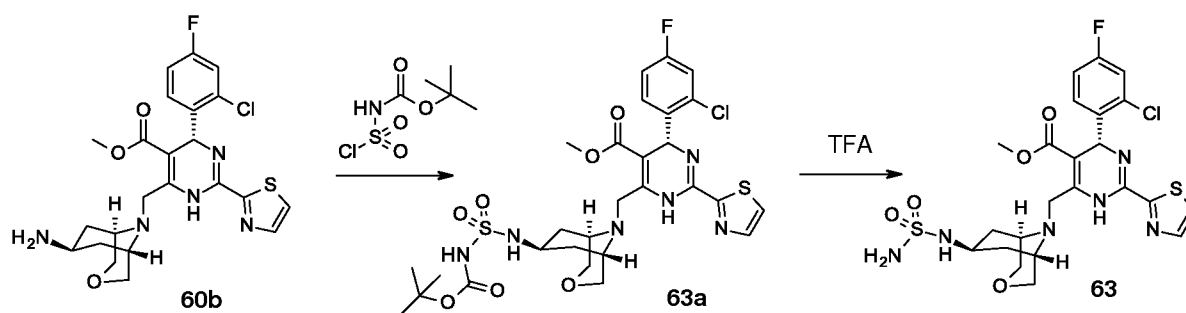
10 Example 63:

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[[(1R,5S)-7-exo-(sulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate



Preparation of Example 63:

-160-



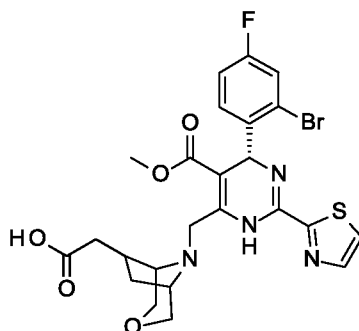
Step I: To a solution of methyl (4R)-6-[[[(1S,5R)-7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-chloro-4-fluorophenyl)-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate **60b** (60 mg, 0.12 mmol) and triethylamine (0.17 mL, 1.2 mmol) in DCM (5 mL) was added a 0.05 M solution of tert-butyl N-chlorosulfonfylcarbamate in DCM (2.5 mL, 0.125 mmol) dropwise at 0 °C. The mixture was allowed to warm to room temperature while stirred for 16 h, and then concentrated in vacuo. The residue was purified by silica gel chromatography to afford 0.08 g of methyl (4R)-6-[[[(1S,5R)-7-(tert-butoxycarbonylsulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-chloro-4-fluorophenyl)-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate **63a** as a yellow oil (yield was 97%). MS: calc'd (MH⁺) 684, measured (MH⁺) 684.

Step II: To a solution of methyl (4R)-6-[[[(1S,5R)-7-(tert-butoxycarbonylsulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-chloro-4-fluorophenyl)-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate **63a** (80 mg, 0.12 mmol) in DCM (5 mL) was added TFA (0.5 mL), The mixture was stirred at 25°C for 3 h, and then concentrated in vacuo. The residue was purified by preparative HPLC to afford 14 mg of the title compound **63** as a light yellow powder (yield was 20%).

Example 64:

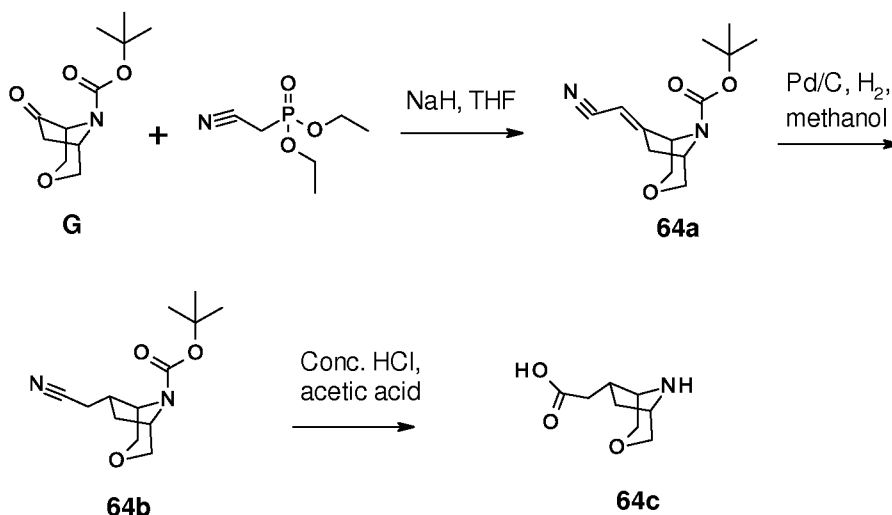
2-[(1R,5S,6S)-8-[[[(4R)-4-(2-bromo-4-fluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]acetic acid

-161-



The title compound was prepared in analogy to compound **1a** in Example 1 starting from methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **53a** (73 mg, 0.15 mmol) and 2-(3-oxa-8-azabicyclo[3.2.1]octan-6-yl)acetic acid (121 mg, 0.7 mmol) **64c**. 21 mg of the title compound was isolated by preparative HPLC as a yellow powder (yield was 16%).

Preparation of 2-(3-oxa-8-azabicyclo[3.2.1]octan-6-yl)acetic acid **64c:**



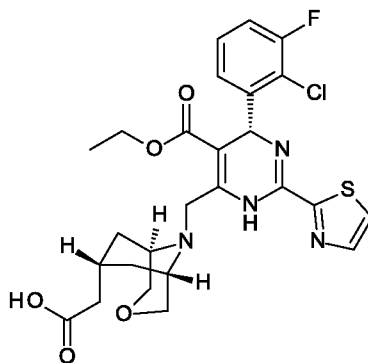
Step I: To a solution of tert-butyl 6-oxo-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate **G** (1.43 mL, 8.81 mmol) in THF (50 mL) was added NaH (350 mg, 8.81 mmol) at ice-bath. After 15 min, 2-diethoxyphosphorylacetonitrile (1 g, 4.4 mmol) was added. The mixture was stirred at 25 °C for 2 h, quenched with water (5 mL) and then extracted with ethyl acetate (200 mL) two times. The combined organic layers were washed with water (200 mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography to afford 970 mg of the product **64a** as a white solid (yield was 88%). MS: calc'd (MH⁺) 251, measured (MH⁺) 251.

Step II: A mixture of tert-butyl (6E)-6-(cyanomethylene)-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate **64a** (970 mg, 3.9 mmol) and 10% palladium on active carbon (200 mg) in methanol (100 mL) was stirred at 25 °C under 30 psi of H₂ pressure for 5 hours. Then the catalyst was filtered off and washed with ethyl acetate. The filtrate was concentrate in vacuo. The residue was purified by silica gel chromatography to afford 180 mg of the product **64b** as a colorless oil (yield was 18%). MS: calc'd (MH⁺) 253, measured (MH⁺) 253.

Step III: A solution of tert-butyl (6S)-6-(cyanomethyl)-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate **64b** (180 mg, 0.71 mmol) in Conc. HCl (5 mL) and acetic acid (1 mL) was stirred at 100 °C for 4 h. Then the mixture concentrated in vacuo to afford 2-[(6S)-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]acetic acid **64c** (121 mg, 99%) which was used for next step without further purification. MS: calc'd (MH⁺) 172, measured (MH⁺) 172.

Example 65:

Endo-2-[(1S,5R)-9-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

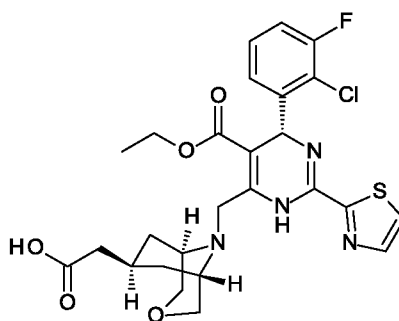


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate, 2-chloro-3-fluoro-benzaldehyde and in the three component reaction step, and (3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (CAS: 1389441-75-1) instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 66:

Exo-2-[(1S,5R)-9-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

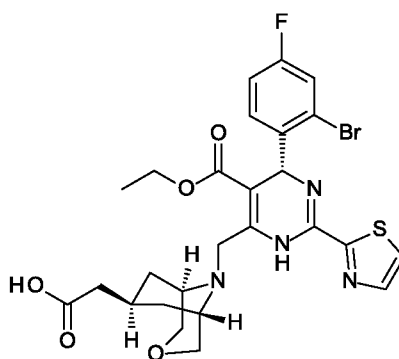
-163-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate, 2-chloro-3-fluoro-benzaldehyde and exo-(3-oxa-9-azabicyclo[3.3.1]non-7-yl)-acetic acid in (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 67:

Exo-2-[(1S,5R)-9-[[4-(2-bromo-4-fluorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

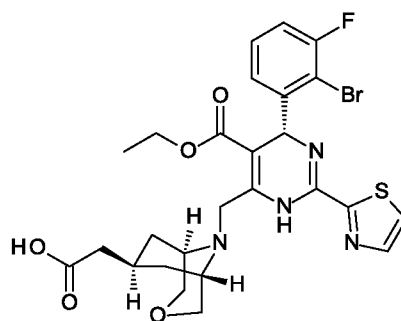


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate and 2-bromo-4-fluoro-benzaldehyde and exo-(3-oxa-9-azabicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 68:

Exo-2-[(1S,5R)-9-[[4-(2-bromo-3-fluorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

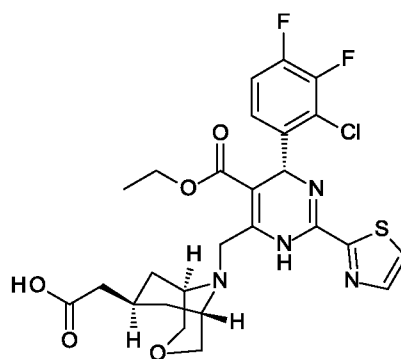
-164-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate, 2-bromo-3-fluoro-benzaldehyde and exo-(3-oxa-9-azabicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 69:

Exo-2-[(1S,5R)-9-[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

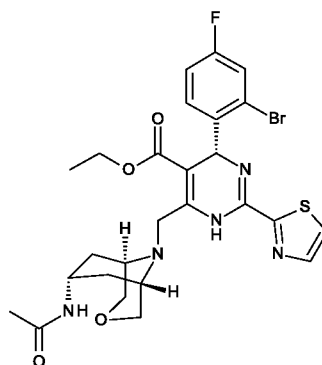


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate, 2-chloro-3,4-difluoro-benzaldehyde and exo-(3-oxa-9-azabicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 70:

Ethyl (4R)-6-[(1S,5R)-7-endo-acetamido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-bromo-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate

-165-

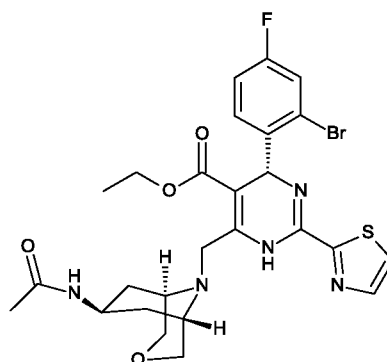


The title compound was prepared in analogy to Example **35** by using ethyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **70a** instead of compound **C**.

- 5 Ethyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **70a** was prepared in analogy to compound **C** with procedures shown in Example **1** by using ethyl acetoacetate and 2-bromo-4-fluoro-benzaldehyde instead of methyl acetoacetate and 2-chloro-4-fluoro-benzaldehyde, respectively..

10 **Example 71:**

Ethyl (4R)-6-[(1S,5R)-7-exo-acetamido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-bromo-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate



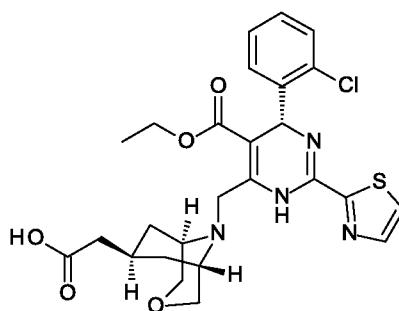
- To a solution of ethyl (4R)-6-[(1S,5R)-7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-bromo-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (75 mg, 0.133 mmol) **71a** and triethylamine (0.06 mL, 0.4 mmol) in DCM (5 mL) was added acetyl chloride (0.018 mL, 0.24 mmol) dropwise at 0 °C. The mixture was allowed to warm to room temperature while stirred for 1 h. Then the mixture was concentrated in vacuo. The residue was purified by preparative HPLC to afford 27 mg of Example **71** as a light yellow powder (yield 20 was 33%).

Preparation of ethyl (4R)-6-[[[(1S,5R)-7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-4-(2-bromo-4-fluoro-phenyl)-2-thiazol-2-yl]-1,4-dihydropyrimidine-5-carboxylate 71a:

Compound **71a** was prepared in analogy to **60b** in Example **60** by using ethyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **70a** instead of compound **C**.

Example 72:

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

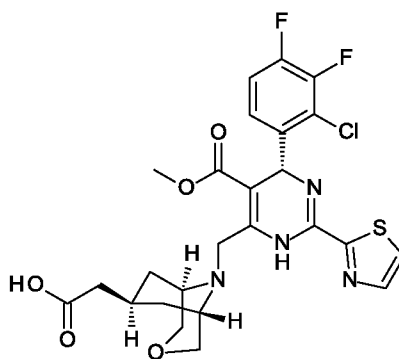


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate, 2-chloro-benzaldehyde and exo-(3-oxa-9-azabicyclo[3.3.1]non-7-yl)-acetic (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 73:

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl)methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

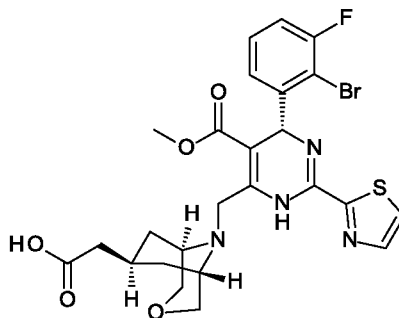
-167-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 2-chloro-3,4-difluoro-benzaldehyde and exo-(3-oxa-9-azabicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 74:

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromo-3-fluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

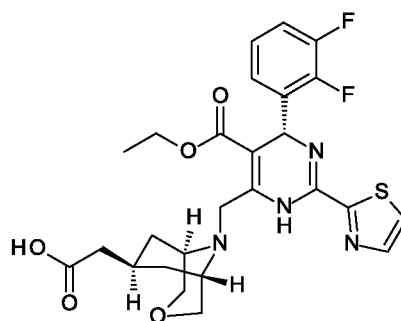


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 2-bromo-3-fluoro-benzaldehyde and exo-(3-oxa-9-azabicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester , respectively.

Example 75:

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2,3-difluorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

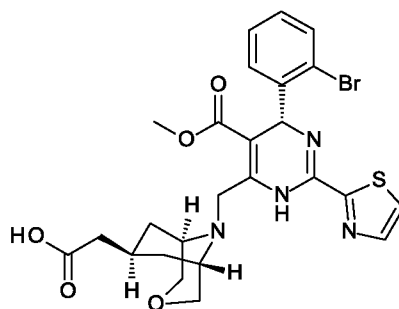
-168-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate, 2,3-difluoro-benzaldehyde and exo-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid instead of methyl acetoacetate, 2-chloro-4-fluoro-
 5 benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 76:

Exo-2-[(1S,5R)-9-[(4R)-4-(2-bromophenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid



10

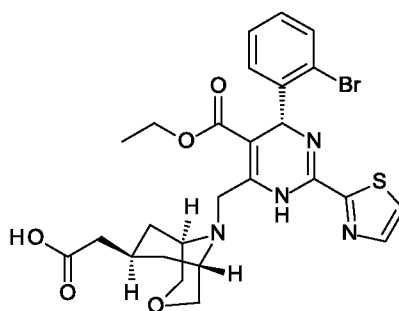
The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 2-bromo-benzaldehyde and exo-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

15

Example 77:

Exo-2-[(1S,5R)-9-[(4R)-4-(2-bromophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

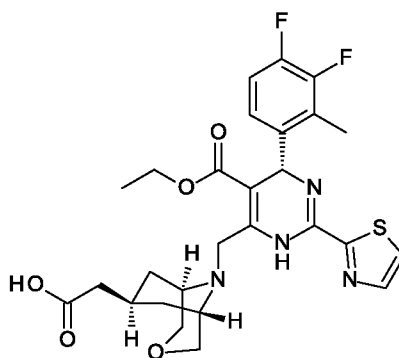
-169-



The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate, 2-bromo-benzaldehyde and exo-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 78:

Exo-2-[(1S,5R)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

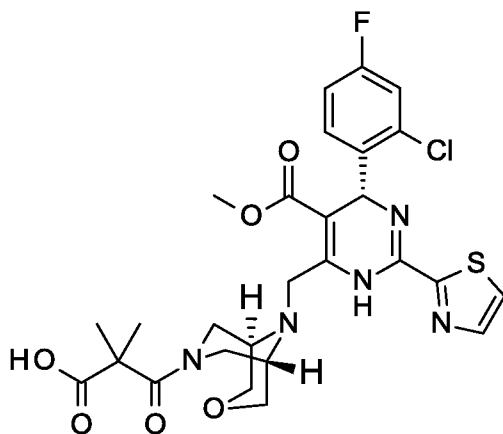


The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate, 2-methyl-3,4-difluoro-benzaldehyde and exo-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Example 79:

3-[(1S,5R)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl]-2,2-dimethyl-3-oxo-propanoic acid

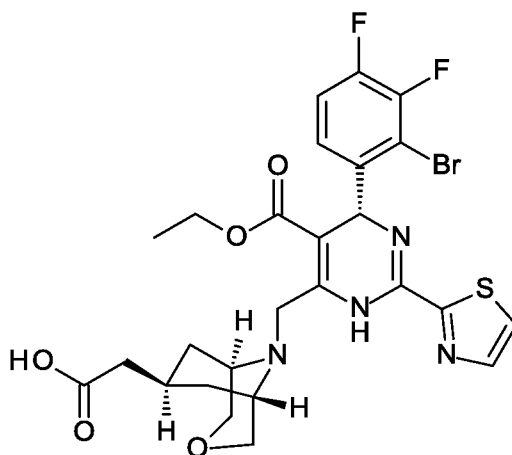
-170-



A mixture of methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (50 mg, 0.1 mmol), 2,2-dimethylpropanedioic acid (prepared as shown in Example 15) (26.4mg, 0.2 mmol), HATU (48 mg, 0.25 mmol) and triethyl-amine (0.09 mL, 0.625 mmol) in dichloromethane (5 mL). The mixture was stirred at 25°C for 16 h, and then concentrated in vacuo. The resulting residue was purified by preparative HPLC to afford 10 mg of the title compound as a white powder (yield was 18%).

Example 80:

Exo-2-[(1S,5R)-9-[(4R)-4-(2-bromo-3,4-difluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

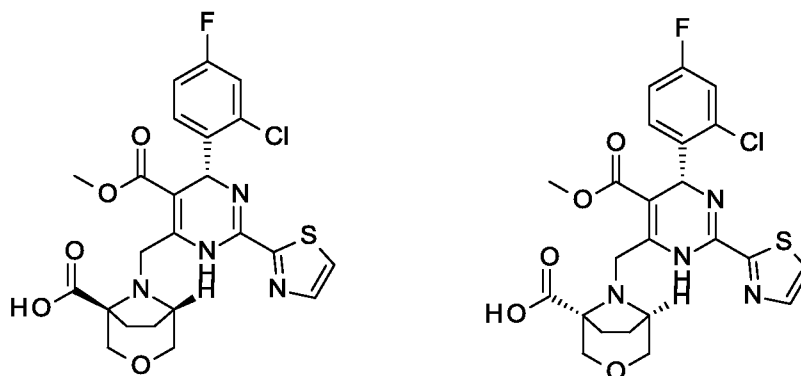


The title compound was prepared in analogy to Example 1a with the procedure shown in Scheme 3 by using ethyl acetoacetate, 2-bromo-3,4-difluoro-benzaldehyde and exo-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PB05416) instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Examples 81 and 82:

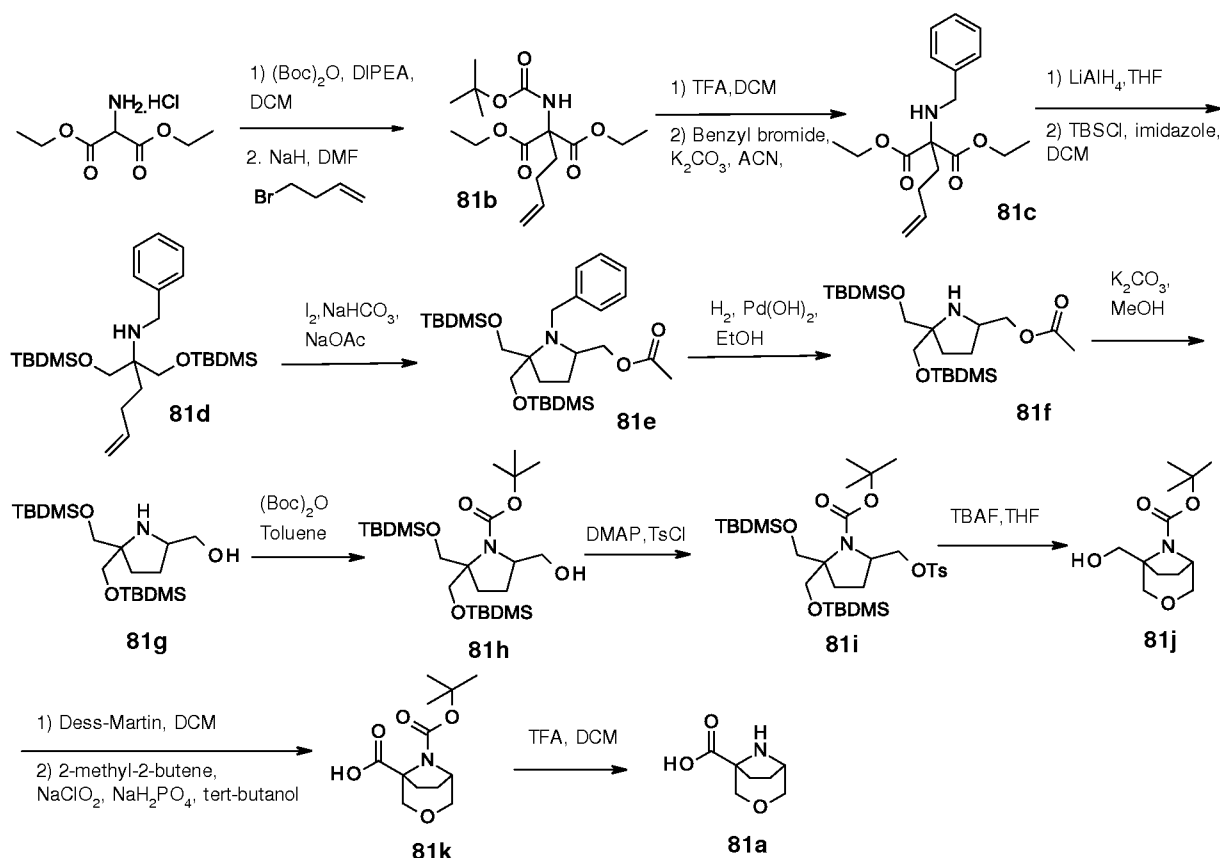
(1*S*,5*R*)-8-[[*(4R)*-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid

5 and (1*R*,5*S*)-8-[[*(4R)*-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid



A mixture of methyl (*(4R)*-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 61 mg, 0.138 mmol), 3-oxa-8-
 10 azabicyclo[3.2.1]octane-5-carboxylic acid **81a** (20 mg, 0.127 mmol) and DIPEA (0.07 mL, 0.4 mmol) in DCM (5 mL) was stirred at 25 °C for 16 h. Then the mixture was concentrated in vacuo. The residue was purified by preparative HPLC to afford a pair of diastereomers, Example 81 and Example 82.

Preparation of 3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid 81a:



Step I. To a solution of diethyl aminomalonate hydrochloride (17 g, 80 mmol) and DIPEA (44 mL, 250 mmol) in DCM (250 mL) was added di-tert-butyl dicarbonate (20.8 g, 96 mmol) at ice-bath. The mixture was allowed to warm to room temperature while stirred for 16 h. Then the mixture was concentrated in vacuo. And the residue was extracted with DCM (150 mL) two times. The combined organic layers were washed with saturated NaHCO₃ (100 mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo to afford 22 g of crude product diethyl 2-(tert-butoxycarbonylamino)propanedioate as a colorless oil (yield was 100%). MS: calc'd (MH⁺) 276, measured (MH⁺) 276.

Step II. To a solution of diethyl 2-(tert-butoxycarbonylamino)propanedioate (20 g, 72.7 mmol) in DMF (100 mL) was added NaH (3.5 g, 87.3 mmol). The mixture was allowed to warm to room temperature while stirred for 0.5 h. Then 4-bromo-1-butene (10.8 g, 80 mmol) was added. The mixture was stirred at 90 °C for 4 h. The mixture was cooled to room temperature, quenched with water (20 mL), and concentrated in vacuo. The residue was purified by silica gel chromatography to afford 14.5 g of the product **81b** as a brown oil (yield was 60%). MS: calc'd (MH⁺) 330, measured (MH⁺) 330.

Step III. To a solution of diethyl 2-but-3-enyl-2-(tert-butoxycarbonylamino)propanedioate **81b** (14.5 g, 4.4 mmol) in DCM (30 mL) was added TFA (10 mL). The mixture was stirred at

room temperature for 16 h, quenched with saturated NaHCO_3 (50 mL) and then extracted with DCM (150 mL) two times, washed with saturated NaHCO_3 (100 mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo to afford diethyl 2-amino-2-but-3-enyl-propanedioate as a crude product (9.5 g, 94%), which was used for next step without further purification. MS: calc'd (MH^+) 230, measured (MH^+) 230.

Step IV. To a mixture of diethyl 2-amino-2-but-3-enyl-propanedioate (9.5 g, 41.5 mmol) and K_2CO_3 (17.3 g, 125 mmol) in ACN (250 mL) was added benzyl bromide (5.9 mL, 49.8 mmol). The mixture was stirred at 80 °C for 16 h. Then the insoluble solid was filtered off and the filtrate was concentrated in vacuo and the residue was extracted with ethyl acetate (200 mL) two times, washed with water (100 mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography to afford 11.3 g of **81c** as a colorless oil (yield was 85%). MS: calc'd (MH^+) 320, measured (MH^+) 320.

Step V. To a mixture of diethyl 2-(benzylamino)-2-but-3-enyl-propanedioate **81c** (13.9 g, 43.6 mmol) in THF (200 mL) was added standard solution of 2 M LiAlH_4 in THF (44 mL) dropwise at ice-bath. The mixture was allowed to warm to room temperature for 3 h. Then the reaction mixture was poured into a mixture of anhydrous sodium sulfate (500 g) and water (50 mL) in ether (300 mL), Then the insoluble solid was filtered off and the filtrate was concentrated in vacuo to afford 2-(benzylamino)-2-but-3-enyl-propane-1,3-diol (9.4 g, 91%) which was used for next step without further purification. MS: calc'd (MH^+) 236, measured (MH^+) 236.

Step VI. To a solution of 2-(benzylamino)-2-but-3-enyl-propane-1,3-diol (9.4 g, 40 mmol) and imidazole (6 g, 88 mmol) in DCM (150 mL) was added a solution of tert-butyldimethylsilyl chloride (16.4 mL, 88 mmol) in DCM (50 mL) dropwise at ice-bath. The mixture was allowed to warm to room temperature while stirred for 16 h. The mixture was quenched with water (100 mL) and then extracted with DCM (100 mL) two times, washed with water (100 mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography to afford 17 g of N-benzyl-1-[tert-butyl(dimethyl)silyl]oxy-2-[[tert-butyl(dimethyl)silyl]oxymethyl]hex-5-en-2-amine **81d** as a white solid (yield was 92%). MS: calc'd (MH^+) 461, measured (MH^+) 461.

Step VII. To a mixture of N-benzyl-1-[tert-butyl(dimethyl)silyl]oxy-2-[[tert-butyl(dimethyl)silyl]oxymethyl]hex-5-en-2-amine (1.2 g, 2.59 mmol), NaHCO_3 (435 mg, 5.18 mmol) and sodium acetate (637 mg, 7.77 mmol) in ACN (100 mL) was added I_2 (658 mg, 2.59 mmol) at room temperature. After 3 h, another batch of sodium acetate (637 mg, 7.77 mmol) was added. The mixture was stirred at 50 °C for 16 h. Then the insoluble solid was filtered off and

the filtrate was concentrated in vacuo. The residue was extracted with ethyl acetate (100 mL) two times, washed with water (100mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash silica gel chromatography to afford 5.7 g of the product **81e** as a brown oil (yield was 45%). MS: calc'd (MH⁺) 522, measured (MH⁺) 522.

Step VIII: The mixture of [1-benzyl-5,5-bis[[tert-butyl(dimethyl)silyl]oxymethyl]pyrrolidin-2-yl]methyl acetate **81e** (5.7 g, 10.94 mmol) and 20% palladium hydroxide on active carbon (1 g) in ethanol (150 mL) was stirred at 50 °C under 2.5 Mpa of H₂ pressure for 16 hours. Then the catalyst was filtered off and washed with ethyl acetate. The filtrate was concentrated in vacuo to afford [5,5-bis[[tert-butyl(dimethyl)silyl]oxymethyl]pyrrolidin-2-yl]methyl acetate **81f** (4.48 g, 95%) which was used for next step without further purification. MS: calc'd (MH⁺) 432, measured (MH⁺) 432.

Step VIII: A mixture of [5,5-bis[[tert-butyl(dimethyl)silyl]oxymethyl]pyrrolidin-2-yl]methyl acetate (4.48 g, 10.4 mmol) and K₂CO₃(g, mmol) in methanol (50 mL) was stirred at 25 °C for 2 h. Then the insoluble solid was filtered off and the filtrate was concentrated in vacuo. And then the residue was extracted with ethyl acetate (50 mL) two times, washed with water (20mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo to afford [5,5-bis[[tert-butyl(dimethyl)silyl]oxymethyl]pyrrolidin-2-yl]methanol **81g** (4 g, 98%) which was used for next step without further purification. MS: calc'd (MH⁺) 390, measured (MH⁺) 390.

Step IX: A mixture of [5,5-bis[[tert-butyl(dimethyl)silyl]oxymethyl]pyrrolidin-2-yl]methanol (2 g, 5.14 mmol) and di-tert-butyl dicarbonate (2.22 g, 10.28 mmol) in toluene (20 mL) was stirred at 90 °C for 4 h. Then the mixture was concentrated in vacuo and the residue was extracted with ether (50 mL) two times, washed with saturated NaHCO₃ (50mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo to afford 4.26 g of the product **81h** as a brown oil (yield was 96%). MS: calc'd (MH⁺) 490, measured (MH⁺) 490.

Step X: To a mixture of tert-butyl 2,2-bis[[tert-butyl(dimethyl)silyl]oxymethyl]-5-(hydroxymethyl)pyrrolidine-1-carboxylate (400 mg, 0.82 mmol) and 4-dimethylaminopyridine (300 mg, 2.45 mmol) in DCM (20 mL) was added 4-toluenesulfonyl chloride (312 mg, 1.64 mmol) at 0 °C. The mixture was stirred at 25°C for 16 h. Then the mixture was diluted with DCM (50 mL) and washed with saturated NH₄Cl (50mL) three times, saturated NaHCO₃ (50mL) three times and water (50mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo to afford tert-butyl 2,2-bis[[tert-butyl(dimethyl)silyl]oxymethyl]-5-(p-

tolylsulfonyloxymethyl)pyrrolidine-1-carboxylate **81i** (410 mg, 77%) which was used for next step without further purification. MS: calc'd (MH⁺) 644, measured (MH⁺) 644.

Step XI: A mixture of tert-butyl 2,2-bis[[tert-butyl(dimethyl)silyl]oxymethyl]-5-(p-tolylsulfonyloxymethyl)pyrrolidine-1-carboxylate (410 mg, 0.64 mmol) and TBAF (1 M in THF, 4 mL) in THF (2 mL) was stirred at 50 °C for 16 h. Then the mixture was diluted with ethyl acetate (50 mL) and washed with saturated NH₄Cl (50mL) three times and water (50mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo to afford isopropyl 5-(hydroxymethyl)-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate **81j** (73 mg, 47%) which was used for next step without further purification. MS: calc'd (MH⁺) 244, measured (MH⁺) 244.

Step XII: To a solution of isopropyl 5-(hydroxymethyl)-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate (73 mg, 0.3 mmol) in DCM (mL) was added Dess-Martin (191 mg, 0.45 mmol) at ice-bath. The mixture was allowed to warm to room temperature while stirred for 2 h. Then the mixture was diluted with DCM (50 mL) and washed with saturated NaHCO₃(50mL) three times and water (50mL) three times, dried over anhydrous sodium sulfate and concentrated in vacuo to afford tert-butyl 5-formyl-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate (71 mg, 98%) which was used for next step without further purification. MS: calc'd (MH⁺) 242, measured (MH⁺) 242.

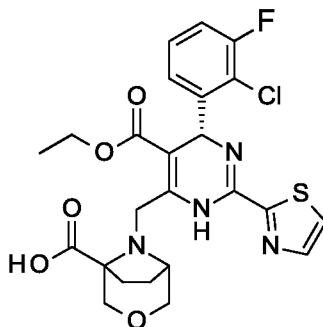
Step XIII: A 50 ml of flask fitted with magnetic stirrer was charged with 5 ml of THF and was cooled to -78 °C, to which 2-methyl-2-butene (0.15 mL, 3 mmol) was added and stirred for 5 minutes. Another 50 ml of flask fitted with magnetic stirrer was charged with tert-butyl 5-formyl-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate (71 mg, 0.3 mmol) and tert butanol (5 mL) and was stirred at 25 °C, to which the above prepared 2-methyl-2-butene THF solution was added. The resulting mixture was cooled to 0 °C, and then a solution of NaH₂PO₄ (81 mg, 0.52mmol) in water (5 mL) and a solution of NaClO₂ (20 mg, 0.22 mmol) in water (5 mL) were added subsequently. After stirring for 20 minutes at 0 °C, the reaction mixture was diluted with water (10 mL), acidified to pH 5~6 using 1N HCl, and extracted with ethyl acetate (50 mL) three times. The combined organic phases were dried over Na₂SO₄, and concentrated in vacuo to afford 8-tert-butoxycarbonyl-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid **81k** (40 mg, 51%), which was used for next step without further purification. MS: calc'd (MH⁺) 258, measured (MH⁺) 258

Step XIV: To a solution of 8-tert-butoxycarbonyl-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid (40 mg, 0.15 mmol) in DCM (3 mL) was added TFA (1 mL), The mixture was stirred at room temperature for 4 h. The mixture was concentrated in vacuo to afford 3-oxa-8-

azabicyclo[3.2.1]octane-5-carboxylic acid **81a** (20 mg, 85%) which was used for next step without further purification. MS: calc'd (MH⁺) 158, measured (MH⁺) 158.

Example 83:

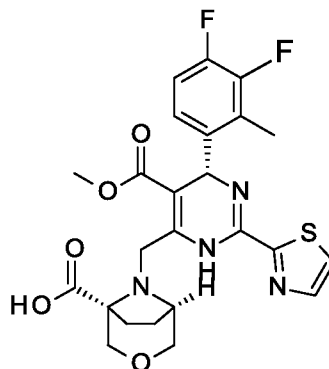
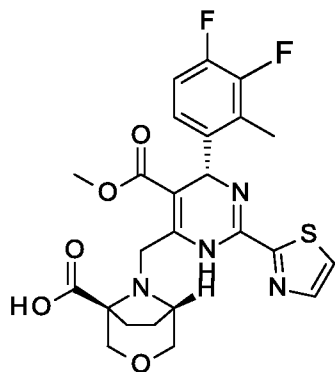
- 5 **8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid**



- The title compound was prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using ethyl acetoacetate, 2-chloro-3-fluoro-benzaldehyde and 3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid **81a** instead of methyl acetoacetate, 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively.

Examples 84 and 85:

- 15 **(1S,5R)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid**
 and **(1R,5S)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid**

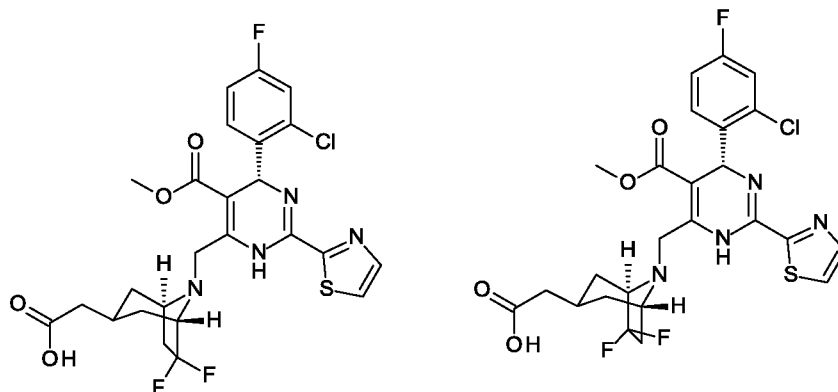


- The title compounds were prepared in analogy to Example **1a** with the procedure shown in Scheme 3 by using 2-methyl-3,4-difluoro-benzaldehyde and 3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid **81a** instead of 2-chloro-4-fluoro-benzaldehyde and 3-oxa-9-

azabicyclo[3.3.1]nonane-7-carboxylic acid methyl ester, respectively. Purification by HPLC afforded two diastereomers, Example **84** and Example **85**.

Examples 86 and 87:

- 5 **2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid and 2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid**



10

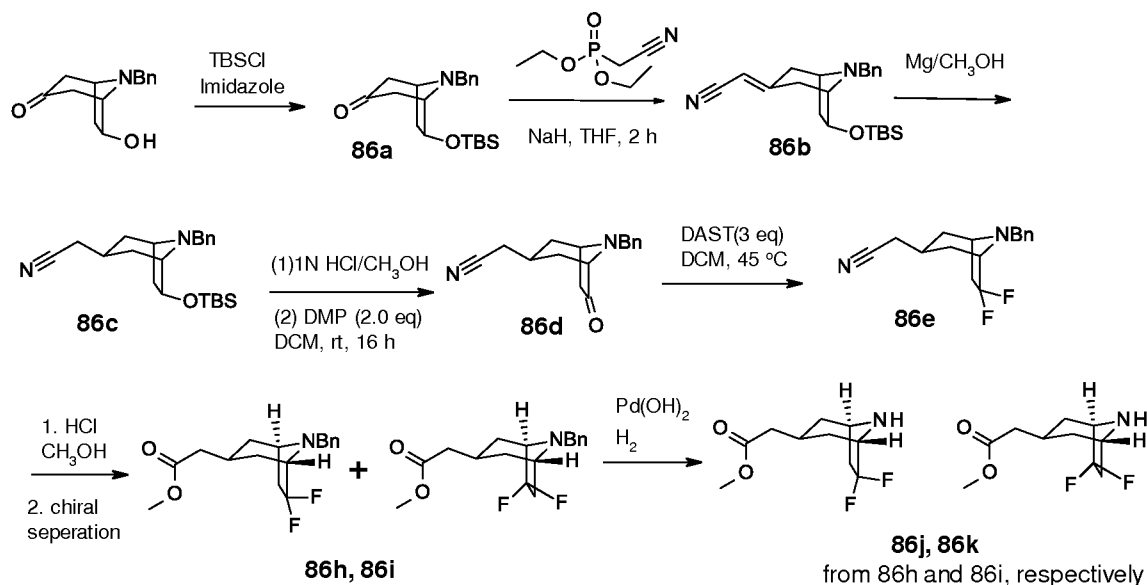
Preparation of Examples 86 and 87:

- To a solution of **86j**, which was one of the two enantiomers of methyl 2-exo-[6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, in dimethylformamide (5 mL) was added methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 76 mg, 0.17 mmol), potassium iodide (35 mg, 0.21 mmol) and N,N-diisopropylethylamine (0.05 mL). The reaction mixture was heated to 55 °C for 3 hours. The reaction mixture was cooled down to room temperature, and then NaOH (35mg, 0.87 mmol) in H₂O (0.5mL) was added. The mixture was then stirred at room temperature for three hours. Afterwards, the reaction mixture was quenched by adding ice-water, and then neutralized to pH 7.0 with 1N hydrochloride solution. The mixture was extracted with ethyl acetate (50 mL) three times. The organic phase was separated and concentrated. The residue was purified by silica gel chromatography and then by prepare-HPLC to give Example **86** (18 mg, 22%).

- Example **87** was prepared in analogy to Example **86** starting from **86k**, which was the other enantiomer of methyl 2-exo-[6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, and methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **C**.

25

Preparation of the two enantiomers of methyl 2-exo-[6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, **86j and **86k**.**



Step I: To a mixture of 8-benzyl-6-hydroxy-8-azabicyclo[3.2.1]octan-3-one (prepared according to the procedure reported in Journal of Heterocyclic Chemistry 1992, 29(6), 1541-4; 46.2 g, 0.2 mol, 1.0 eq) and imidazole (16.3 g, 0.24 mol, 1.2 eq) in DCM (500 mL) was added TBSCl (33.1 g, 0.22 mol, 1.1 eq) in DCM (100 mL) slowly at room temperature in 10 min, then the mixture was stirred at room temperature for 2 h, washed with water (300 mL) and brine (300 mL), the organic layer was dried over Na₂SO₄ and concentrated to give 8-benzyl-6-[tert-butyl(dimethyl)silyl]oxy-8-azabicyclo[3.2.1]octan-3-one **86a** as a colorless oil, 62 g, yield: 90%. MS: calc'd (MH⁺) 232, measured (MH⁺) 232.

Step II: To a suspension of NaH (6.98 g, 173 mmol) in tetrahydrofuran (460 mL) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (18.5 mL, 103.8 mmol) in tetrahydrofuran (80 mL). The reaction was refluxed for 1 hour and then cooled at 0 °C again. To the reaction mixture was added a solution of compound **86a** (26.0 g, 75 mol) in tetrahydrofuran (80 mL). The reaction was allowed to warm up to room temperature and stirred 2 hours. The reaction mixture was then quenched with saturated aqueous solution of NaHCO₃, and most of the THF was removed under reduced pressure. Ethyl acetate (200 mL) was added, washed with water, brine, dried over Na₂SO₄ and evaporated to dryness. The residue was purified on silica gel, eluting with 0 to 20% EtOAc in hexanes, to give the desired product (2E)-2-[8-benzyl-6-[tert-butyl(dimethyl)silyl]oxy-8-azabicyclo[3.2.1]octan-3-ylidene]acetonitrile **86b** (27 g, 98%). MS: calc'd (MH⁺) 369, measured (MH⁺) 369.

Step III: A solution of compound **86b** (27.8 g, 75.3 mmol) in anhydrous methanol (300 mL) was placed in a flask equipped with a condenser, to it was added Mg (2 g, 87 mmol). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then cooled with ice-water bath. After another 1 h stirring, another batch of Mg (2 g, 87 mmol) was added, and the reaction mixture was allowed to stir for 2 hours at 0 °C. The mixture was diluted with ethyl acetate (500 mL), and quenched by adding slowly 12 N HCl (13 mL). The solvents were removed under reduced pressure, and the residue was dissolved in ethyl acetate (500 mL), which was then washed with water, brine, dried over Na₂SO₄ and evaporated to dryness. The above procedure was repeated until compound **86b** was completely consumed. A crude product (14 g) with 2-exo-[8-benzyl-6-[tert-butyl(dimethyl)silyl]oxy-8-azabicyclo[3.2.1]octan-3-yl]acetonitrile **86c** as the major product was obtained, and used without further purification in the next step. Around 20% of the endo-isomer was observed.

Step IV: The crude **86c** (14 g) was dissolved in 1N HCl in methanol (350 mL). The reaction mixture was stirred at room temperature for 4 hours. The solvent was evaporated under reduced pressure. Ethyl acetate (300 mL) and water (50 mL) were added, and basified with 2N NaOH aqueous solution to pH 10. The organic phase was separated and the aqueous phase was extracted with ethyl acetate 3 times. The combined organic layers were washed with brine, dried over MgSO₄ and evaporated to dryness. The residue was dissolved in DCM (200 mL), and DMP (23 g, 56.5 mmol) was added. After stirred overnight, 20 mL of water was added, and the solid in the reaction mixture was filtered off. The filtrate was extracted with DCM. The organic layers were combined and washed with water, brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified on silica gel, eluting with 0 to 50% EtOAc in hexanes, to give the desired product 2-exo-(8-benzyl-6-oxo-8-azabicyclo[3.2.1]octan-3-yl)acetonitrile **86d** (8 g). Around 10% of the endo-isomer was observed.

Step V: To a stirred solution of compound **86d** (8g, 31.3 mmol) in 20 mL of dichloromethane was added diethylaminosulfur trifluoride (12 mL, 94 mmol). The mixture was stirred at 50 °C overnight, then quenched with saturated NaHCO₃ aqueous solution at 0 °C, and extracted three times with DCM (100 mL). The combined organic layers were washed with water, brine, dried over anhydrous MgSO₄, filtered, concentrated and purified by silica gel column chromatography (EtOAc/Hexane 5:95) to yield 2-exo-(8-benzyl-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl)acetonitrile **86e** (7 g, 81%).

Step VI: Acetyl chloride (48 mL) was added into methanol (100 mL) at 0 °C, and the mixture was stirred at room temperature for 1 hour. To it was added compound **86e** (2 g, 7.2

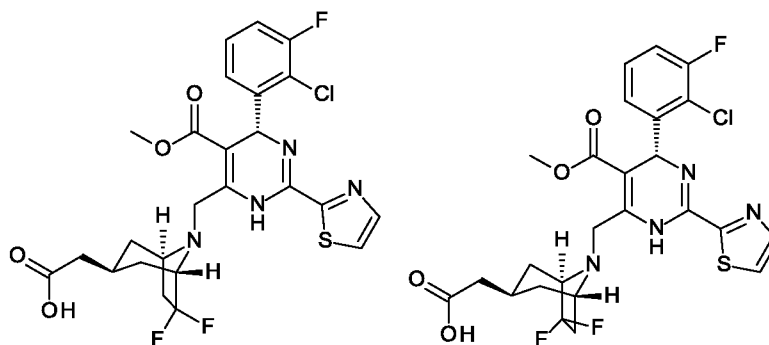
mmol), and the resulting mixture was stirred for 18 hours at 80 °C. After cooling to room temperature, the solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate, neutralized carefully with aqueous NaHCO₃ solution. The organic phase was washed with brine, dried over Na₂SO₄ and evaporated to dryness. The crude mixture was purified on silica gel to give methyl 2-exo-(8-benzyl-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl)acetate (2 g, 88%), which was further purified by chiral SFC (ChiralCel OJ 250*30mm, 5µm 15% ethanol) to give a pair of enantiomers of methyl 2-exo-[8-benzyl-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, **86h** (peak 1) and **86i** (peak 2).

Step VII: To a solution of **86h** (2g 6.4 mmol) in 15 mL of methanol was added 200 mg of Pd(OH)₂ (20% loading on carbon, wet with 50% water content). The mixture reaction was stirred at room temperature under 1 atm H₂ for 6 h, and then filtered, and washed with additional methanol. The filtrates were concentrated under reduced pressure to yield one of the two enantiomers of methyl 2-exo-[6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, **86j** (1.26g).

The other enantiomer of methyl 2-exo-[6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, **86k**, was prepared in analogy to **86j** from **86i**.

Examples 88 and 89:

2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid and 2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid



Preparation of Examples 88 and 89:

Example **88** was prepared in analogy to Example **86** starting from **86j** (30 mg) and methyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **88a** (76 mg). 18 mg of the title compound **88** was isolated after purification by

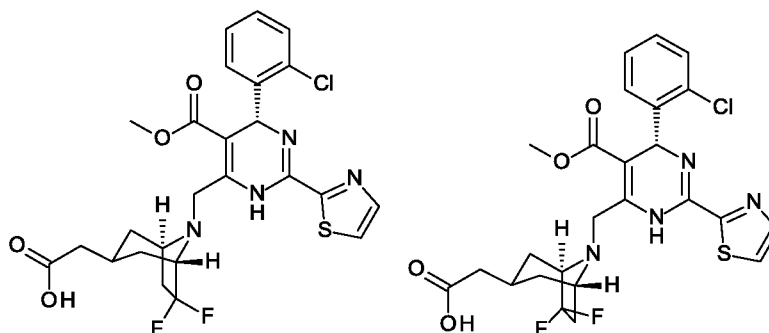
preparative HPLC. Methyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **88a** was prepared in analogy to compound **C** with procedures shown in Example 1 by using 2-chloro-3-fluoro-benzaldehyde instead of 2-chloro-4-fluoro-benzaldehyde in the three component reaction.

5 Example **89** was prepared in analogy to Example **86** starting from **86k** (30 mg) and methyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **88a** (76 mg). 14 mg of compound **89** was isolated after purification by preparative HPLC.

10 **Examples 90 and 91:**

2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chlorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid
and 2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chlorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid

15



Preparation of Examples 90 and 91:

Example **90** was prepared in analogy to Example **86** starting from **86j** and methyl (4R)-6-(bromomethyl)-4-(2-chlorophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **90a**.

20 Methyl (4R)-6-(bromomethyl)-4-(2-chlorophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **90a** was prepared in analogy to compound **C** with procedures shown in Example 1 by using 2-chlorobenzaldehyde instead of 2-chloro-4-fluoro-benzaldehyde in the three component reaction.

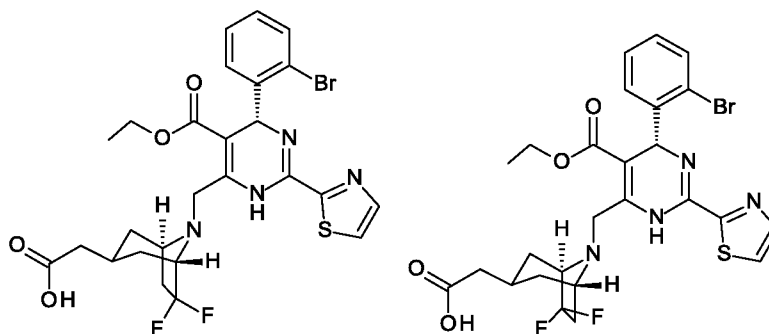
Example **91** was prepared in analogy to Example **86** starting from **86k** and methyl (4R)-6-(bromomethyl)-4-(2-chlorophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **90a**.

25

Examples 92 and 93:

2-[(1R,3S,5S)-8-[[[(4R)-4-(2-bromophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid
and 2-[(1S,3R,5R)-8-[[[(4R)-4-(2-bromophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid

5



Preparation of Examples 92 and 93:

Example **92** was prepared in analogy to Example **86** starting from **86j** and ethyl (4R)-6-(bromomethyl)-4-(2-bromophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **92a**.

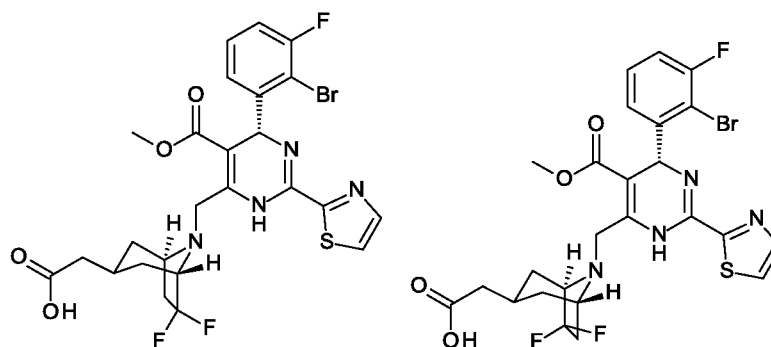
10 (4R)-6-(bromomethyl)-4-(2-bromophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **92a** was prepared in analogy to compound **C** with procedures shown in Example **1** by using ethyl acetoacetate and 2-bromobenzaldehyde instead of methyl acetoacetate and 2-chloro-4-fluoro-benzaldehyde in the three component reaction.

Example **93** was prepared in analogy to Example **86** starting from **86k** and ethyl (4R)-6-(bromomethyl)-4-(2-bromophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **92a**.

Examples 94 and 95:

2-[(1R, 3S,5S)-8-[[[(4R)-4-(2-bromo-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid
20 and 2-[(1S, 3R,5R)-8-[[[(4R)-4-(2-bromo-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid

-183-



Preparation of Examples 94 and 95:

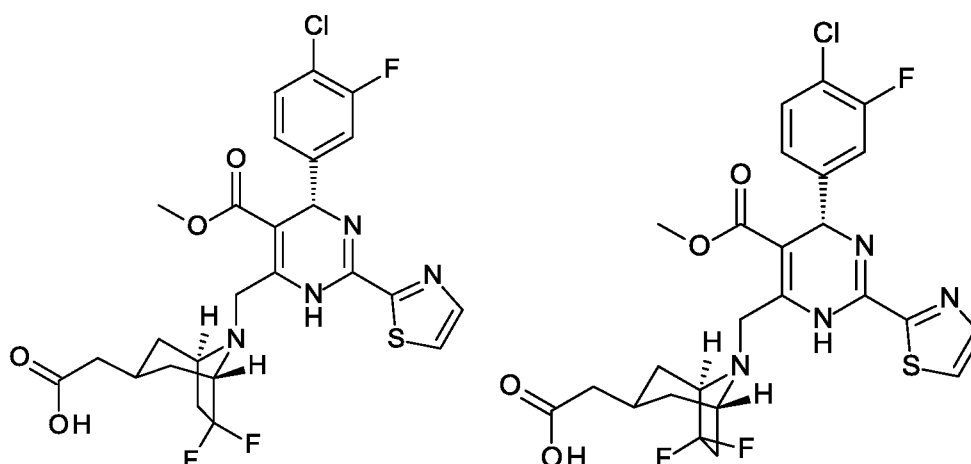
Example **94** was prepared in analogy to Example **86** starting from **86j** (30 mg) and methyl (4R)-4-(2-bromo-3-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **94a** (86 mg). 13 mg of the title compound was isolated.

Methyl (4R)-4-(2-bromo-3-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **94a** was prepared in analogy to compound **C** with procedures shown in Example **1** by using 2-bromo-3-fluorobenzaldehyde instead of 2-chloro-4-fluorobenzaldehyde.

Example **95** was prepared in analogy to Example **86** starting from **86k** (30 mg) and methyl (4R)-4-(2-bromo-3-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **94a** (86 mg). 56 mg of the title compound was isolated.

Examples 96 and 97:

2-[(1R,3S,5S)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid and 2-[(1S,3R,5R)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid



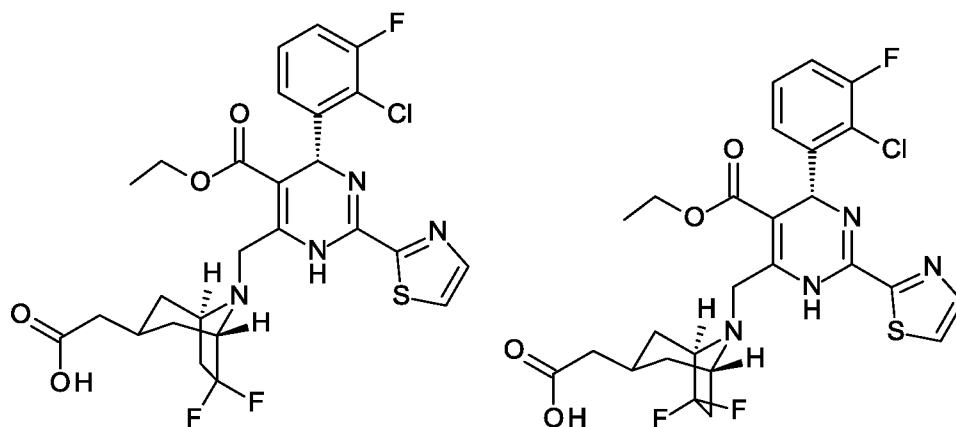
Preparation of Examples 96 and 97:

Example **96** was prepared in analogy to Example **86** starting from **86j** (30 mg) and methyl (4S)-6-(bromomethyl)-4-(4-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **96a** (78 mg). 12 mg of Example **96** was isolated. Methyl (4S)-6-(bromomethyl)-4-(4-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **96a** was prepared in analogy to compound **C** with procedures shown in Example **1** by using 4-chloro-3-fluorobenzaldehyde instead of 2-chloro-4-fluoro-benzaldehyde in the three component reaction step.

Example **97** was prepared in analogy to Example **86** starting from **86k** (30 mg) and methyl (4S)-6-(bromomethyl)-4-(4-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **96a** (78 mg). 14 mg of the title compound was isolated.

Examples 98 and 99:

2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid and **2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid**



Preparation of Examples 98 and 99:

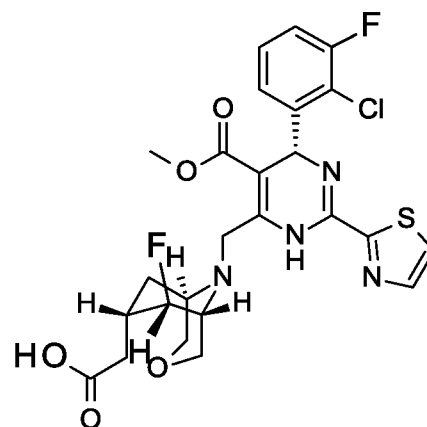
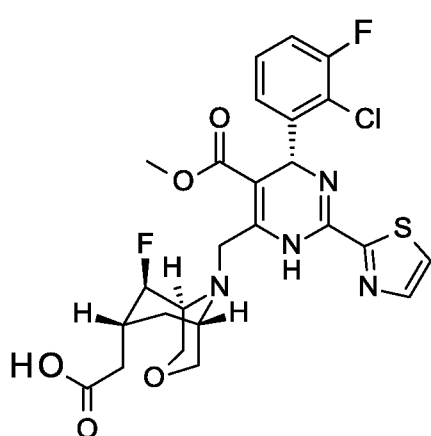
Example **98** was prepared in analogy to Example **86** starting from **86j** (30 mg) and ethyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **98a** (80 mg). 25 mg of Example **98** was isolated. Ethyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **98a** was prepared in analogy to compound **C** with procedures shown in Example **1** by using ethyl acetoacetate and 2-chloro-3-fluorobenzaldehyde instead of methyl acetoacetate and 2-chloro-4-fluoro-benzaldehyde, respectively.

Example **99** was prepared in analogy to Example **86** starting from **86k** (30 mg) and ethyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **98a** (80 mg). 25 mg of the title compound was isolated.

Examples 100 and 101:

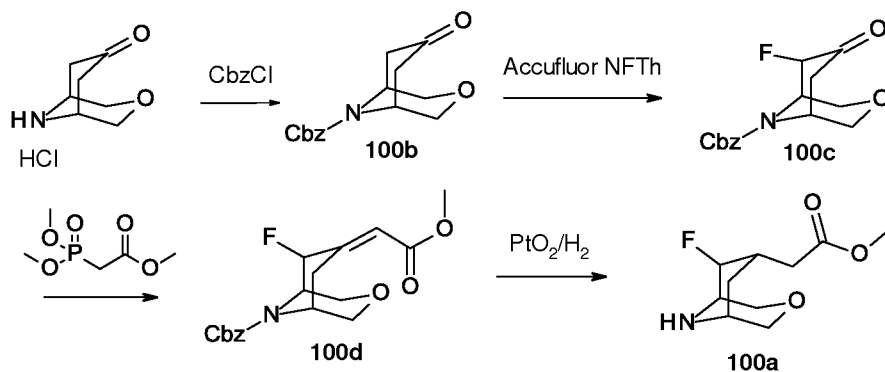
2-[(1S,5S,6R,7R)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

and 2-[(1R,5R,6S,7S)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid



The title compounds were prepared in analogy to Example **86** starting from methyl 2-(6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **100a** (100 mg) and methyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **88a** (208 mg). The crude product was purified by silica gel chromatography first, and then by preparative HPLC to give Example **101** and Example **102**.

Preparation of methyl 2-(6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate 100a:



Step I: 3-oxa-9-azabicyclo[3.3.1]nonan-7-one hydrochloride (CAS 1126795-00-3) (10 g) was dissolved in 200 ml of dichloromethane which was cooled to 0°C. Then, CbzCl (14.3 g, 84.7 mmol) was added to the mixture followed by the dropwise addition of a solution of TEA (14.6 ml, 112.8 mmol) in 20 ml of dichloromethane. The mixture was allowed to warm up to room temperature. After stirring 2 h, it was quenched with 20 ml of a saturated aqueous solution of NaHCO₃. The two layers were separated and the aqueous layer was extracted with dichloromethane (3x150 ml). The combined organic layers were washed with water, dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silica gel, yielding 10.1 g of benzyl 7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **100b** (64%).

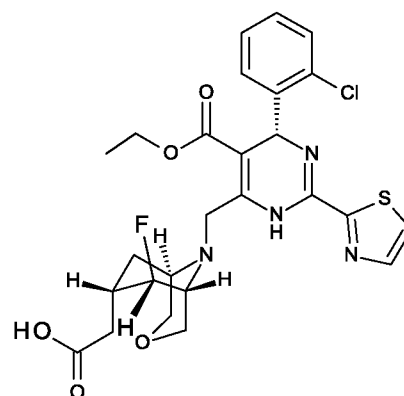
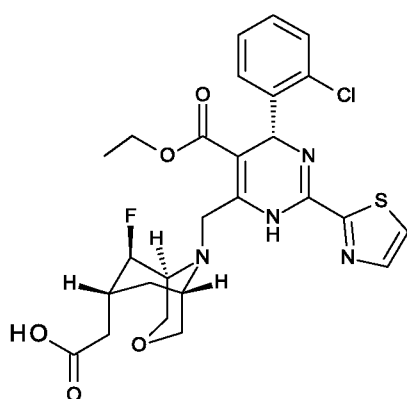
Step II: To a solution of benzyl 7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **100b** (7.6 g, 27.6 mmol) in methanol (150 mL) at 0 °C was added Accufluor NFTh (17.5 g, 55.2 mmol). The reaction was stirred at 90 °C for 3 hours and then cooled to room temperature. After filtration, the filtrate was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (20 mL), washed with water and brine, dried over Na₂SO₄ and evaporated to dryness. The crude mixture was purified on silica gel, eluting with 0 to 50% EtOAc in hexanes, to give the desired product benzyl 6-fluoro-7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **100c** (4.1 g, 50%). MS: calc'd (MH⁺) 294, measured (MH⁺) 294.

Step III: To a solution of NaH (273 mg, 11.4 mmol) in tetrahydrofuran (30 mL) at 0 °C was added dropwise a solution of methyl 2-dimethoxyphosphorylacetate (2.1 g, 11.4 mmol) in tetrahydrofuran (10 mL). The reaction was stirred at 70 °C for 1 hour and then cooled to 0 °C again. To the reaction mixture was added a solution of benzyl 6-fluoro-7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **100c** (1.7 g, 5.7 mmol) in tetrahydrofuran (8 mL). The reaction was allowed to warm up to room temperature and stirred 2 hours. After being quenched with 1 N HCl, the solvent was evaporated under reduced pressure. Ethyl acetate (20 mL) was added. The mixture was washed with water, brine, dried over Na₂SO₄ and evaporated to dryness. The crude mixture was purified on silica gel, eluted with 0 to 20% EtOAc in hexanes, to give the desired product benzyl (7Z/E)-6-fluoro-7-(2-methoxy-2-oxo-ethylidene)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **100d** (1.8 g, 89%). MS: calc'd (MH⁺) 350, measured (MH⁺) 350.

Step IV: To a solution of (7Z/E)-6-fluoro-7-(2-methoxy-2-oxo-ethylidene)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **100d** (1.8 g, 5.1 mmol) in THF (50 ml) and H₂O (2 ml) was added PtO₂ (250 mg, 1.1 mmol). The mixture reaction was stirred at room temperature under hydrogen balloon for 6 h, then filtered and washed with additional THF. The filtrates were concentrated under reduced pressure to yield methyl 2-(6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **100a** (910 mg, 70%).

Examples 102 and 103

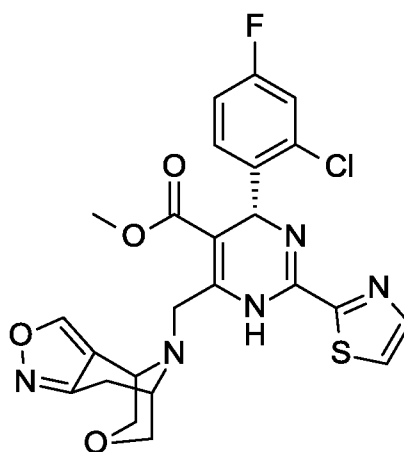
2-[(1S,5S,6R,7R)-9-[[[(4R)-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid and 2-[(1R,5R,6S,7S)-9-[[[(4R)-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid



The title compounds were prepared in analogy to Example **86** starting from methyl 2-(6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **100a** (100 mg) and ethyl (4R)-6-(bromomethyl)-4-(2-chloro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **102a** (215 mg). The crude product was purified by silica gel chromatography first, and then by preparative HPLC to give Example **102** (27 mg), and Example **103** (21 mg). Ethyl (4R)-6-(bromomethyl)-4-(2-chloro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **102a** was prepared in analogy to compound **C** with procedures shown in Example **1** by using ethyl acetoacetate and 2-chloro-benzaldehyde instead of methyl acetoacetate and 2-chloro-4-fluoro-benzaldehyde in the three component reaction.

Example 104:

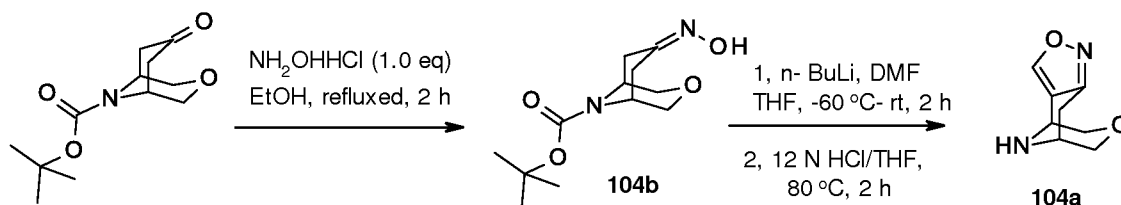
(4R)-4-(2-Chloro-4-fluoro-phenyl)-6-(4,10-dioxo-5,12-diazatricyclo[6.3.1.0*2,6*]dodeca-2,5-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared in analogy to Example **1a** in Scheme 3 by using methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-

carboxylate **C** (200 mg) and 4,10-Dioxa-5,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2,5-diene **104a** (100 mg). 15 mg of the title compound was isolated as yellow powder.

Preparation of 4,10-Dioxa-5,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2,5-diene 104a:

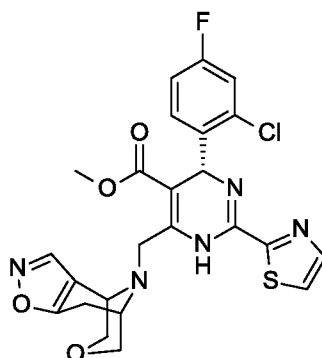


Step I: A solution of tert-butyl 7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (482 mg, 2 mmol, 1.0 eq) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (462 mg, 3 mmol, 3.0 eq) in EtOH (10 mL) was refluxed for 2 h. The reaction mixture was concentrated to give tert-butyl 7-hydroxyimino-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **104b** as a white solid, which was used in next step without further purification. MS: calc'd (MH^+) 267, measured (MH^+) 267.

Step II: To a solution of compound **104b** (512 mg, 2 mmol, 1.0 eq) in THF (10 mL) was added n-BuLi (5 mL, 2.0 M, 5.0 eq) dropwise at $-50\text{ }^\circ\text{C}$. After 30 min, dry DMF (740 mg, 10 mmol, 5.0 eq) in THF (2 mL) was added dropwise, the mixture was stirred for another 2 h from $-60\text{ }^\circ\text{C}$ to room temperature. To it 12 N HCl (1 mL) was added and refluxed for 2 h. The reaction mixture was concentrated to give 4,10-Dioxa-5,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2,5-diene **104a** (332 mg) as an oil. MS: calc'd (MH^+) 167, measured (MH^+) 167.

Example 105:

(4R)-4-(2-Chloro-4-fluoro-phenyl)-6-(5,10-dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared in analogy to Example **1a** in Scheme 3 by using methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-

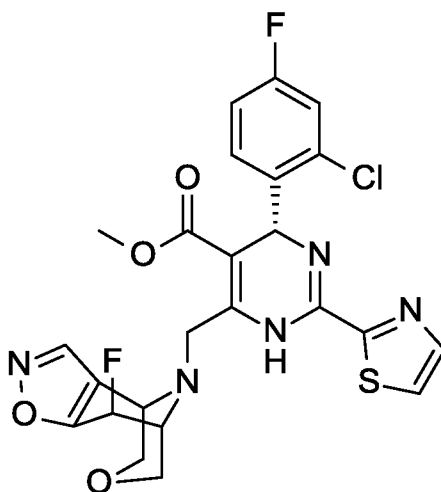
carboxylate **C** (200 mg) and 5,10-Dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene **105a** (100 mg). 20 mg of the title compound was isolated as yellow powder.

Preparation of 5,10-Dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene 105a:

A solution of tert-butyl 7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (482 mg, 2 mmol) and tert-butoxy-N,N,N',N'-tetra-methyl-methanedi-
 5 amine (522 mg) in dioxane (10 mL) was stirred at 60 °C for 16 h. The solvent was removed in vacuo, and the residue was dissolved in EtOH (10 mL). To it NH₂OH·HCl (462 mg, 3 mmol) was added. After stirring at room temperature for 2 h, 12 N HCl (1 mL) was added and refluxed for 2 h. The reaction mixture was concentrated to give 5,10-Dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene **105a** as
 10 an oil (yield 100%), which was used without further purification. MS: calc'd (MH⁺) 167, measured (MH⁺) 167.

Example 106:

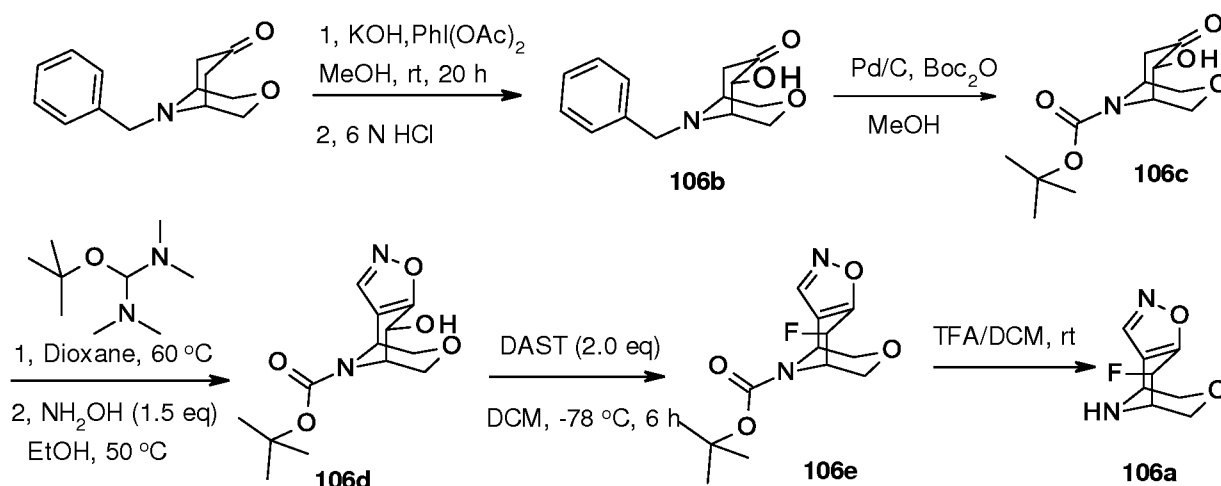
(4R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-fluoro-5,10-dioxa-4,12-diaza-
 15 tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester



The title compound was prepared in analogy to Example **1a** in Scheme 3 by using methyl
 (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-
 20 carboxylate **C** (200 mg) and 7-fluoro-5,10-dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene **106a** (140 mg). 8 mg of the title compound was isolated as yellow powder.

Preparation of 7-fluoro-5,10-dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien 106a:

-191-



Step I: To a stirred solution of potassium hydroxide (730 mg, 13 mmol) in dry MeOH (50 mL) at 0 °C under nitrogen was added a solution of 9-benzyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one (CAS: 81514-40-1, 1 g, 4.3 mmol) in dry MeOH (20 mL) dropwise over 10 min. The reaction mixture was stirred at 0 °C for another 10 min, and PhI(OAc)₂ (1.83 g, 5.5 mmol) was added portion wise over 10 min. The reaction mixture was warmed to room temperature, with stirring, overnight. After the starting material disappeared as monitored by TLC, MeOH was removed under reduced pressure and the residue was cooled to 0 °C and 10 ml of 6N HCl was added carefully. The mixture was stirred at room temperature for 2 hours, and then ethyl acetate and water (50 mL, 1: 1) were added. The aqueous layer was separated and was added into K₂CO₃ till the solution was saturated. The mixture was extracted with ethyl acetate (20 mL) three times, dried and concentrated, the residue was purified by silica gel (EA/PE= 1: 2) to give 9-benzyl-6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-one **106b** as colorless oil, 270 mg, yield: 25%. MS: calc'd (MH⁺) 248, measured (MH⁺) 248.

Step II: A mixture of compound **106b** (247 mg, 1 mmol, 1.0 eq), Boc₂O (654 mg, 3 mmol, 3.0 eq) and Pd/C (50 mg, 20%) in MeOH (10 mL) was stirred at room temperature for 16 h. Then the solid was filtered off, the solvent was removed in vacuo, the residue was purified by silica gel (EA/PE= 1: 1) to give tert-butyl 6-hydroxy-7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **106c** as a colorless oil. 260 mg, yield: 100%. MS: calc'd (MH⁺) 258, measured (MH⁺) 258.

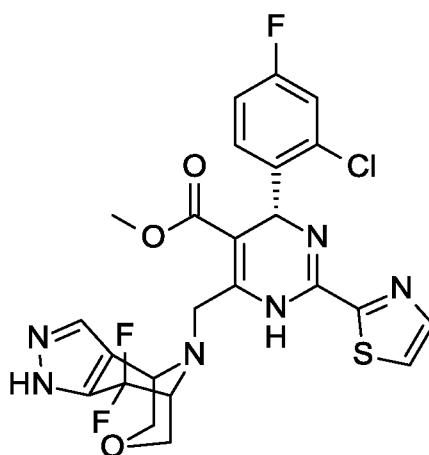
Step III: 7-Hydroxy-5,10-dioxo-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene-12-carboxylic acid tert-butyl ester **106d** was prepared in analogy to compound **105a** in Example 105, starting with **106c** (260 mg). 141 mg of **106d** was obtained as a colorless oil. MS: calc'd (MH⁺) 283, measured (MH⁺) 283.

Step IV: To a solution of 7-Hydroxy-5,10-dioxo-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene-12-carboxylic acid tert-butyl ester **106d** (141 mg, 0.5 mmol, 1.0 eq) in DCM (5 mL) was added DAST (166 mg, 1 mmol, 2.0 eq) at -78 °C. Then mixture was stirred for 6 h from -78 °C to room temperature. The reaction was diluted with EA (20 mL), and washed with aqueous NaHCO₃ (5%, 20 mL). The organic layer was dried and concentrated to give 7-Fluoro-5,10-dioxo-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene-12-carboxylic acid tert-butyl ester as an oil, 150 mg, crude yield: 100%. MS: calc'd (MH⁺) 285, measured (MH⁺) 285.

Step V: A solution of 7-Fluoro-5,10-dioxo-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene-12-carboxylic acid tert-butyl ester (150 mg) in TFA/DCM (5 mL, 1:2) was stirred at room temperature for 1 h. The solvent was removed in vacuo to give 7-fluoro-5,10-dioxo-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene **106a** (141 mg) as yellow oil, crude yield: 100%. MS: calc'd (MH⁺) 185, measured (MH⁺) 185.

Example 107:

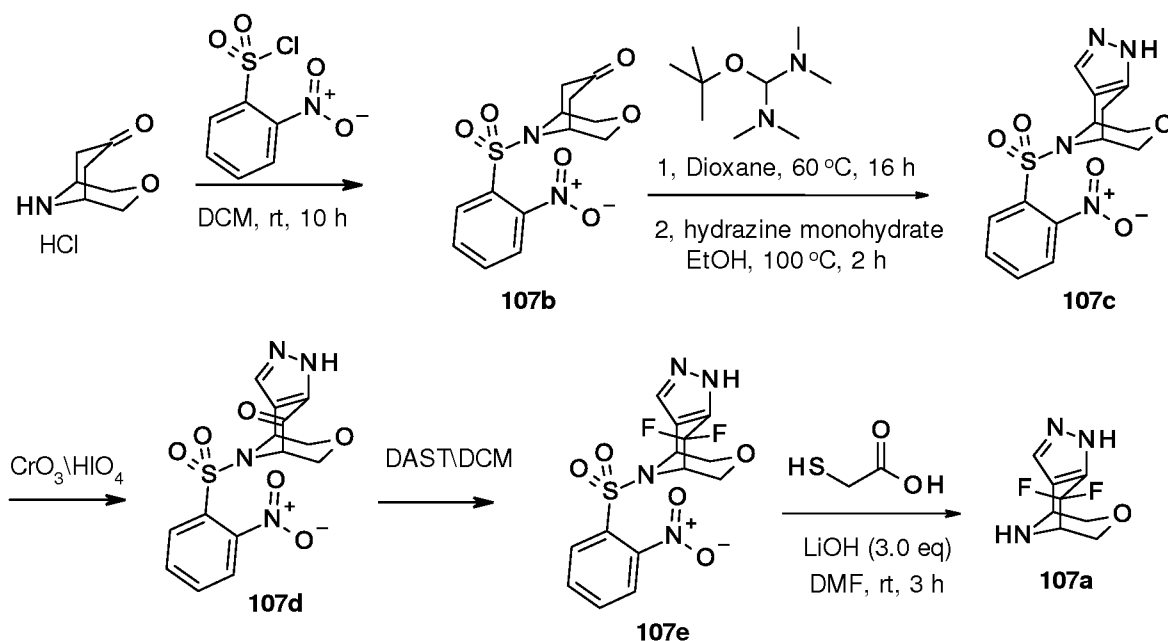
(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7,7-difluoro-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester



The title compound was prepared in analogy to Example **1a** in Scheme 3 by using methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **C** (100 mg) and 7,7-difluoro-5,10-dioxo-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene **107a** (50 mg). 8 mg of the title compound was isolated as yellow powder.

Preparation of 7,7-difluoro-5,10-dioxo-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene **107a:**

-193-



Step I: A solution of 3-oxa-9-azabicyclo[3.3.1]nonan-7-one hydrochloride (CAS 1126795-00-3, 2.82 g), TEA (6.12 g, 60 mmol, 3.0 eq) and 2-Nitro-benzenesulfonyl chloride (8.84 g, 40 mmol, 2.0 eq) in DCM (100 mL) was stirred at room temperature for 10 h. Then the solvent was removed in vacuo, the residue was purified by silica gel (EA/PE= 1: 3) to give 9-(2-nitrophenyl)sulfonyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one **107b** as a white solid, 4.90 g, yield: 75%. MS: calc'd (MH^+) 327, measured (MH^+) 327.

Step II: A mixture of compound **107b** (4.9 g, 15 mmol, 1.0 eq) and tert-butoxy-N,N,N',N'-tetra-methyl-methanediamine (3.92 g, 22.5 mmol, 1.5 eq) in dioxane (50 mL) was stirred at 60 °C for 16 h, then the solvent was removed in vacuo, the residue was dissolved in EtOH (50 mL), $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (3.5 mg, 75 mmol, 5.0 eq) was added and then stirred at 60 °C for 2 h. The reaction mixture was concentrated and then purified by silica gel (EA/PE= 1: 2) to give 12-(2-Nitro-benzenesulfonyl)-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene **107c** as a slight yellow oil, 1.57 g, yield: 29.8%. MS: calc'd (MH^+) 351, measured (MH^+) 351.

Step III: A solution of CrO_3 (100 mg, 1.0 mmol, 0.33 eq) and H_5IO_6 (2.05 g, 9 mmol, 3.0 eq) in MeCN (50 mL) was stirred at room temperature for 5 min, compound **107c** (1.05 g, 3 mmol, 1.0 eq) in MeCN (5 mL) was added and then stirred at 70 °C for 12 h. The solid was filtered off and the filtrate was diluted with EA (50 mL), washed with $\text{Na}_2\text{S}_2\text{O}_3$ (10%, 50 mL) and brine (50 mL). The organic layer was concentrated, and the residue was purified by silica gel (EA/PE= 1: 2) to give 12-(2-nitro-benzenesulfonyl)-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-7-one **107d** as a white solid, 270 mg, yield: 25%. MS: calc'd (MH^+) 365, measured (MH^+) 365.

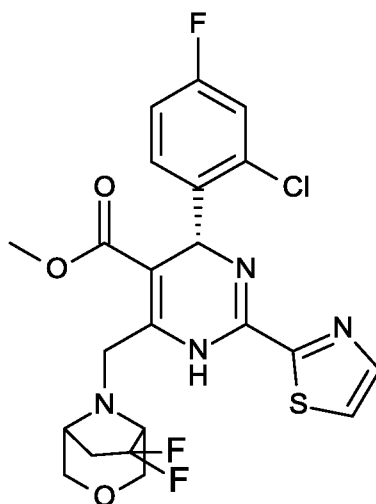
Step IV: A mixture of compound **107d** (270 mg, 0.74 mmol, 1.0 eq) and DAST (1 mL, 7.4 mmol, 10.0 eq) in DCM (1 mL) was stirred at 60 °C in sealed tube for 18 h. The mixture was added dropwise to a cooled aqueous NaHCO₃ (20 mL, 5%) solution, then the mixture was extracted with EA (20 mL) two times, the organic layer was dried (Na₂SO₄) and concentrated.

5 The residue was purified by silica gel (EA/PE= 1: 3) to give 7,7-difluoro-12-(2-nitro-benzenesulfonyl)-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene **107e** as a slight yellow oil. 100 mg, yield: 35%. MS: calc'd (MH⁺) 387, measured (MH⁺) 387.

Step V: To a mixture of compound **107e** (100 mg, 0.26 mmol, 1.0 eq) and LiOH (33 mg, 0.78 mmol, 3.0 eq) in DMF (5 mL) was added mercaptoacetic acid (36 mg, 0.4 mmol, 1.5 eq)
10 slowly, the mixture was stirred at room temperature for 3 h. The solvent was removed in vacuo to give 7,7-difluoro-5,10-dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-diene **107a** as an oil, used in next step without further purification. MS: calc'd (MH⁺) 202, measured (MH⁺) 202.

Example 108:

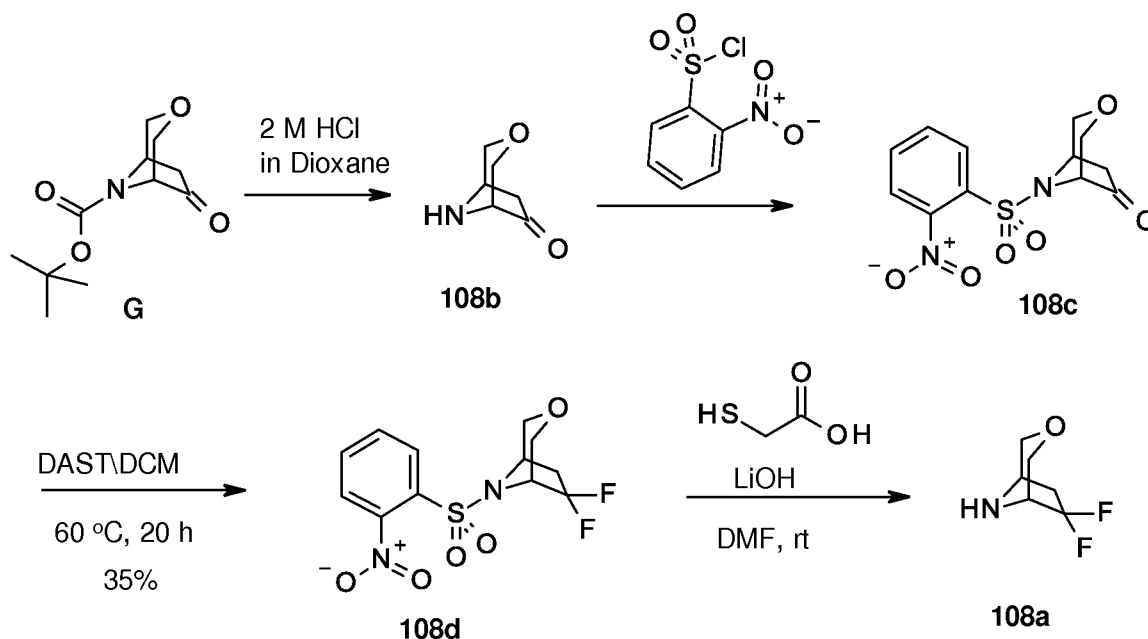
15 **Methyl (4R)-4-(2-chloro-4-fluorophenyl)-6-[(6,6-difluoro-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-(1,3-thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate**



The title compound was prepared in analogy to Example **1a** in Scheme 3 by using methyl
20 (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 100 mg) and 6,6-difluoro-3-oxa-8-azabicyclo[3.2.1]octane **108a** (200 mg). 6 mg of the title compound was isolated as yellow powder.

Preparation of 6,6-difluoro-3-oxa-8-azabicyclo[3.2.1]octane **108a**:

-195-



Step I: A mixture of compound **G** (227 mg, 1 mmol, 1.0 eq) in HCl/Dioxane (2 mL) was stirred at room temperature for 2 h. Then the solvent was removed in vacuo to give 3-oxa-8-azabicyclo[3.2.1]octan-6-one **108b** as white solid (200 mg), which was used in the next step without further purification. MS: calc'd (MH⁺) 128, measured (MH⁺) 128.

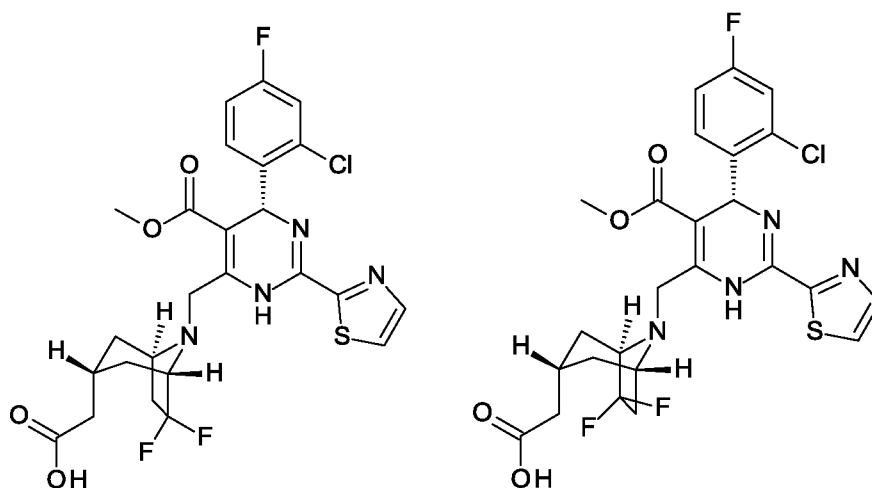
Step II: A mixture of compound **108b** (100 mg), TEA (102 mg), K₂CO₃ (207 mg, 1.5 mmol, 3.0 eq) and 2-nitro-benzenesulfonyl chloride (222 mg) in MeCN (10 mL) was stirred at room temperature for 10 h. Then the solvent was removed in vacuo, the residue was purified by silica gel (EA/PE= 1: 3) to give 8-(2-nitrophenyl)sulfonyl-3-oxa-8-azabicyclo[3.2.1]octan-6-one **108c** as a white solid, 100 mg. MS: calc'd (MH⁺) 313, measured (MH⁺) 313.

Step III: A mixture of compound **108c** (100 mg) and DAST (1 mL) in DCM (1 mL) was stirred at 50 °C in sealed tube for 18 h. The mixture was added dropwise to a cooled aqueous NaHCO₃ (20 mL, 5%) solution, then the mixture was extracted with EA (20 mL) two times, the organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by silica gel (EA/PE= 1: 3) to give 6,6-difluoro-8-(2-nitrophenyl)sulfonyl-3-oxa-8-azabicyclo[3.2.1]octane **108d** as a slight yellow oil. 90 mg. MS: calc'd (MH⁺) 335, measured (MH⁺) 335.

Step IV: To a solution of compound **108d** (90 mg) and LiOH (36 mg) in DMF (5 mL) was added mercaptoacetic acid (36 mg) slowly, the mixture was stirred at room temperature for 3 h. The solvent was removed in vacuo to give 6,6-difluoro-3-oxa-8-azabicyclo[3.2.1]octane **108a** as an oil, which was used in next step without purification. MS: calc'd (MH⁺) 150, measured (MH⁺) 150.

Examples 109 and 110:

2-[(1R,3R,5S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid
 and 2-[(1S,3S,5R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid

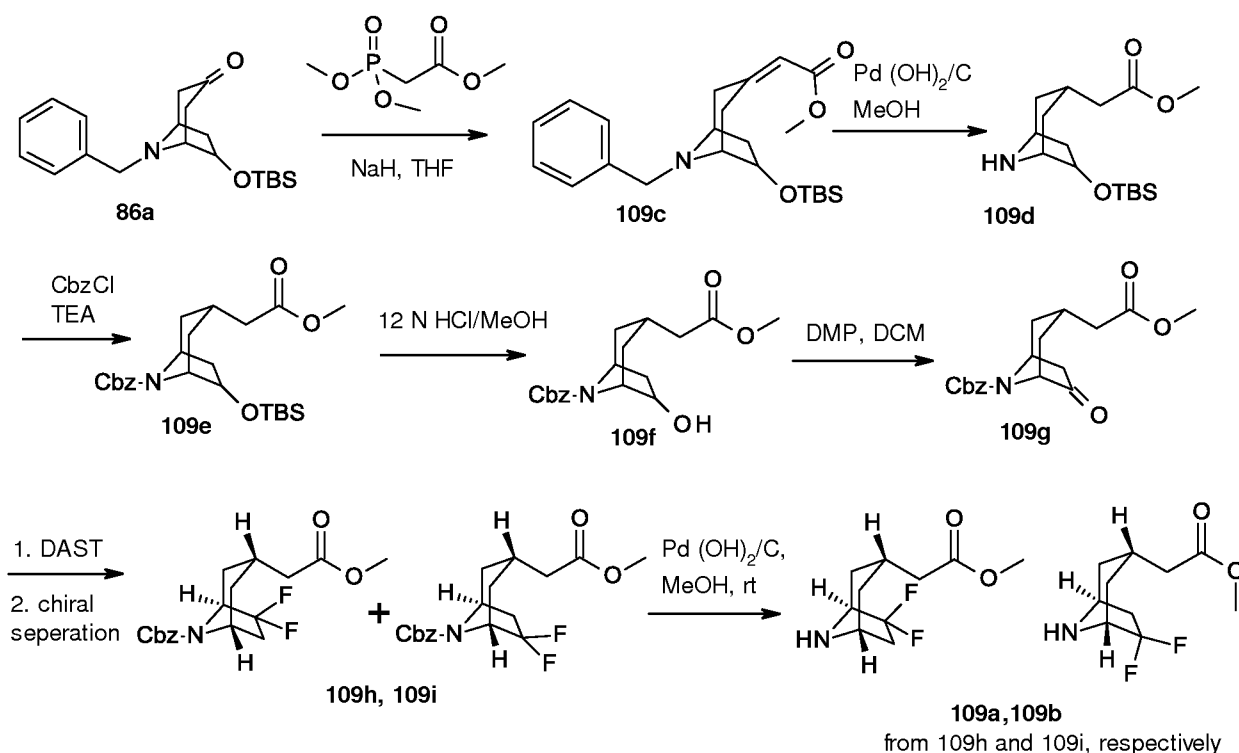
**Preparation of Examples 109 and 110:**

Example **109** was prepared in analogy to Example **86** by using (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 45 mg) and **109a** (one of the two enantiomers of methyl 2-endo-[6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, 22 mg). 22 mg of Example **109** was isolated as yellow powder.

Example **110** was prepared in analogy to Example **86** by using (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 44 mg) and **109b** (the other enantiomer of methyl 2-endo-[6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, 22 mg). 20 mg of Example **110** was isolated as yellow powder.

Preparation of the two enantiomers of methyl 2-endo-[6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, 109a and 109b:

-197-



Step I: To a solution of Trimethyl phosphoroacetate (36.4 g, 0.2 mol, 2.0 eq) in THF (800 mL) was added NaH (8 g, 0.2 mol, 2.0 eq) slowly at room temperature, then the mixture was refluxed for 1 h. After the reaction was cooled to room temperature, compound **86a** (34.5 g, 0.1 mol, 1.0 eq) in THF (150 mL) was added dropwise and then refluxed for 16 h. The mixture was quenched with water, extracted with EA (500 mL) two times, the organic layers were combined, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel (EA/PE= 1: 10) to give methyl (2E/Z)-2-[8-benzyl-6-[tert-butyl(dimethyl)silyl]oxy-8-azabicyclo[3.2.1]octan-3-ylidene]acetate **109c** as a white solid, 34 g, yield: 85%. ¹H NMR (400MHz, DMSO-d₆) δ: 7.45-7.11 (m, 5H), 5.75 (s, 0.6H), 5.70 (s, 0.4H), 4.13-3.99 (m, 1H), 3.99-3.82 (m, 2H), 3.66-3.53 (m, 3H), 3.52-3.45 (m, 1H), 3.45 (br, 1H), 3.35-3.29 (m, 1H), 3.07 (br, 1H), 2.53 (br, 1H), 2.27 (d, J = 15.6 Hz, 0.4H), 2.13 (d, J = 14.0 Hz, 0.6H), 1.94-1.76 (m, 2H), 0.91-0.81 (m, 9H), 0.06-0.07 (m, 6H); MS: calc'd (MH⁺) 402, measured (MH⁺) 402.

Step II: A mixture of compound **109c** (32 g, 0.08 mol, 1.0 eq) and Pd(OH)₂/C (3 g, 15%) in MeOH (800 mL) was stirred at 60 °C for 20 h under 1 atm hydrogen, then the mixture was filtered, the filtrate was concentrated to give methyl 2-[6-[tert-butyl(dimethyl)silyl]oxy-8-azabicyclo[3.2.1]octan-3-ylidene]acetate **109d** as a colorless oil, 22.4 g, yield: 90%. ¹H NMR (400MHz, DMSO-d₆) δ: 4.21 (dd, J = 1.8, 6.4 Hz, 1H), 3.58 (s, 3H), 3.45 (t, J = 6.8 Hz, 1H), 3.03 (d, J = 6.0 Hz, 1H), 2.31-2.24 (m, 2H), 2.17-2.08 (m, 1H), 2.03 (dd, J = 6.0, 13.6 Hz, 1H),

1.98-1.82 (m, 2H), 1.53 (dd, J = 7.8, 13.6 Hz, 1H), 1.10-0.95 (m, 2H), 0.89-0.84 (m, 9H), 0.07-0.02 (m, 6H); MS: calc'd (MH⁺) 312, measured (MH⁺) 312.

Step III: To a solution of compound **109d** (40 g, 0.13 mol, 1.0 eq) and TEA (40 g, 0.39 mol, 3.0 eq) in DCM (800 mL) was added a solution of CbzCl (45 g, 0.26 mol, 2.0 eq) in DCM (150 mL) slowly. The resulting mixture was stirred at room temperature for 16 h. The mixture was quenched with water, washed with 1N HCl (500 mL), the organic layer was dried over Na₂SO₄ and concentrated to give benzyl 6-[tert-butyl(dimethyl)silyl]oxy-3-(2-methoxy-2-oxo-ethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate **109e** as a crude product.

Step IV: crude **109e** was dissolved in MeOH (400 mL), 12 N HCl (40 mL, 3.0 eq) was added and then stirred at room temperature for 30 min. The mixture was diluted with water (800 mL), and extracted two times with EA (500 mL). The organic layers were combined, dried over Na₂SO₄ and concentrated, the residue was purified by silica gel (EA/PE= 1: 3) to give benzyl 6-hydroxy-3-(2-methoxy-2-oxo-ethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate **109f** as a colorless oil, 30 g, yield for two steps, 70%. ¹H NMR (400MHz, DMSO-d₆) δ: 7.43-7.26 (m, 5H), 5.09 (s, 2H), 4.90 (dd, J = 3.6, 6.8 Hz, 1H), 4.23 (d, J = 6.4 Hz, 1H), 4.16-4.09 (m, 1H), 4.12-3.92 (m, 1H), 3.59 (s, 3H), 2.38 (d, J = 7.2 Hz, 2H), 2.14-1.93 (m, 5H), 1.72 (br, 1H); MS: calc'd (MH⁺) 334, measured (MH⁺) 334.

Step V: To a solution of compound **109f** (30 g, 0.09 mol, 1.0 eq) in DCM (800 mL) was added DMP (Dess-Martin Periodinane, 76.5 g, 0.18 mol, 2.0 eq) slowly at 0 °C. The resulting mixture was stirred at room temperature for 16 h, and quenched with water. The solid was filtered off, the filtrate was washed with brine (500 mL), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel (EA/PE= 1: 3) to give benzyl 3-(2-methoxy-2-oxo-ethyl)-6-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate **109g** as a colorless oil (26.5 g, yield 88%). ¹H NMR (400MHz, DMSO-d₆) δ: 7.46-7.30 (m, 5H), 5.15 (s, 2H), 4.61 (br, 1H), 4.00 (br, 1H), 3.58 (s, 3H), 2.77 (dd, J = 7.2, 18.2 Hz, 1H), 2.41-2.30 (m, 3H), 2.28-2.10 (m, 3H), 1.49 (d, J = 13.2 Hz, 1H), 1.38 (d, J = 11.8 Hz, 1H); MS: calc'd (MH⁺) 332, measured (MH⁺) 332.

Step VI: A mixture of compound **109g** (16 g, 0.04 mol, 1.0 eq) and DAST (32 g, 0.2 mol, 5.0 eq) in DCM (30 mL) was stirred at 60 °C in sealed tube for 3 days. The mixture was added dropwise to a cooled aqueous NaHCO₃ (500 mL, 5%) solution, then the mixture was extracted with EA (300 mL) two times, the organic layers were combined, washed with 1N HCl (200 mL) and brine (300 mL), dried over Na₂SO₄ and concentrated. The crude product contained the desired difluorinated product and a byproduct, vinyl fluoride in a ratio of about 1:1. The crude product was dissolved in DCM (200 mL), to it m-CPBA (20 g, 0.12 mol, 3.0 eq) was added

slowly. The reaction mixture was stirred at room temperature for 16 h. the solid was filtered off, the filtrate was washed with NaHCO₃ (200 mL, 5% aq. solution) three times, Na₂S₂O₃ (200 mL, 5% aqueous solution) two times and brine (300 mL). The organic layer was concentrated and purified by preparative HPLC to remove the epoxide derived from vinyl fluoride. The obtained difluoro-product was further purified by chiral SFC (ChiralPak AD 250*30mm, 5µm, 15% ethanol) to give a pair of enantiomers of benzyl 6,6-difluoro-3-endo-(2-methoxy-2-oxo-ethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate, **109h** (2g, peak 1), and **109i** (2g, peak 2).

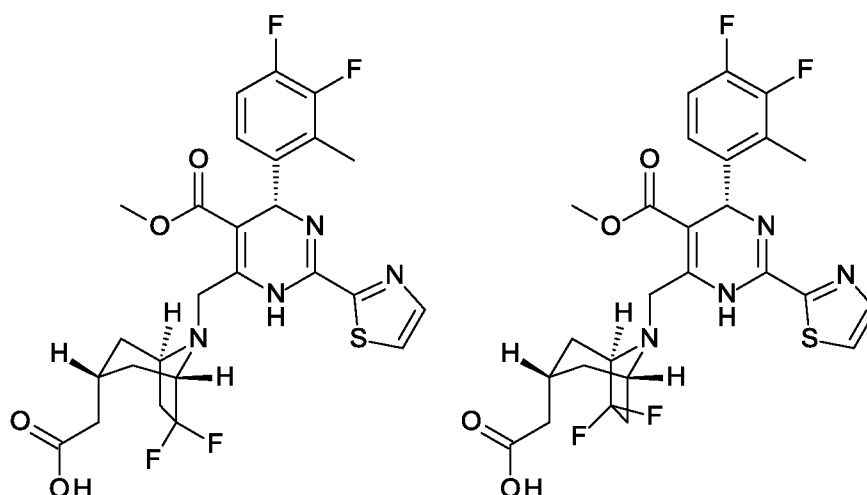
Step VII: A mixture of **109h** (2 g, 5.5 mmol, 1.0 eq) and Pd(OH)₂/C (200 mg, 10%) in MeOH (30 mL) was stirred at room temperature for 16 h under hydrogen, then the mixture was filtered, the filtrate was concentrated to give one of the two enantiomers of methyl 2-endo-[6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, **109a**, as a colorless oil (1.15 g, yield 92%). ¹H NMR (400MHz, DMSO-d₆) δ: 3.58 (s, 3H), 3.47 (t, J = 7.4 Hz, 1H), 3.29-3.18 (m, 1H), 2.77 (br, 1H), 2.37-2.16 (m, 4H), 2.12-1.85 (m, 3H), 1.36 (dd, J = 7.0, 14.2 Hz, 1H), 1.10 (dd, J = 6.4, 13.6 Hz, 1H); ¹⁹F NMR (376MHz, DMSO-d₆) d = (-87.44) - (-89.12) (m, 1F), (-107.59) - (-109.06) (m, 1F). MS: calc'd (MH⁺) 220, measured (MH⁺) 220.

The other enantiomer of methyl 2-endo-[6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetate, **109b**, was prepared from **109i** in analogy to **109a**.

Examples 111 and 112:

2-[(1R,3R,5S)-8-[[4S]-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid

and 2-[(1S,3S,5R)-8-[[4S]-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid



Preparation of Examples 111 and 112:

Example **111** was prepared in analogy to Example **86** starting from methyl (4S)-6-(bromomethyl)-4-(3,4-difluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **111a** (50 mg) and **109a** (22 mg). 4 mg of Example **111** was isolated as yellow powder.

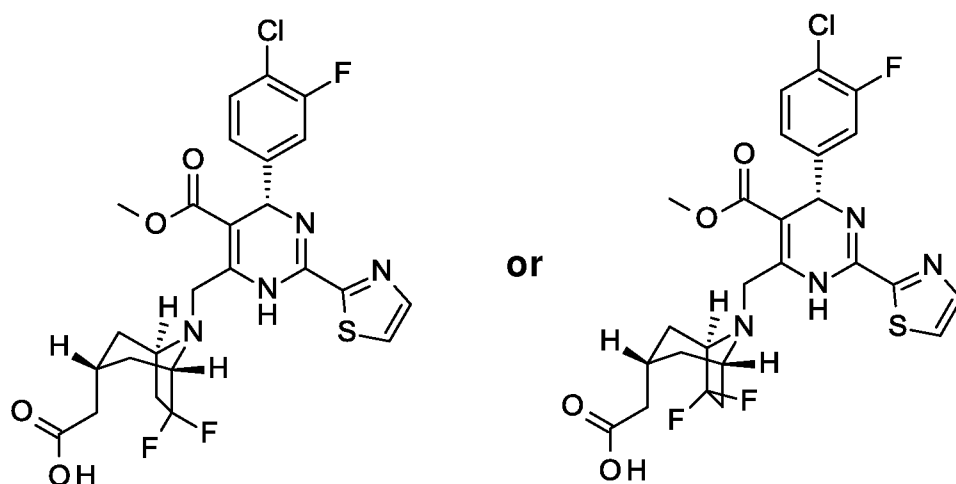
Methyl (4S)-6-(bromomethyl)-4-(3,4-difluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **111a** was prepared in analogy to compound **C** with procedures shown in Example **1** by using 3,4-difluoro-2-methyl-benzaldehyde instead of 2-chloro-4-fluoro-benzaldehyde .

Example **112** was prepared in analogy to Example **86** starting from methyl (4S)-6-(bromomethyl)-4-(3,4-difluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **111a** (50 mg) and **109b** (22 mg). 3.5 mg of Example **112** was isolated as yellow powder.

Example 113:

2-[(1R,3R,5S)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid or 2-[(1S,3S,5R)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid

-201-

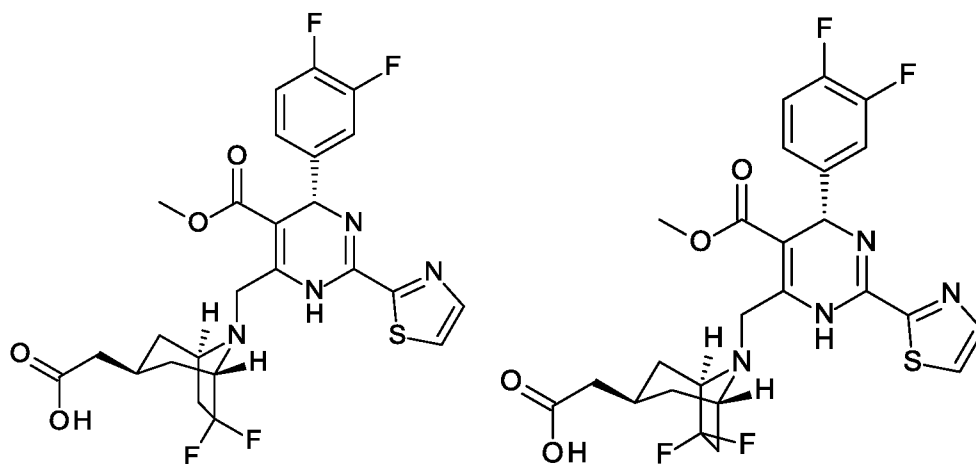


The title compound was prepared in analogy to Example **86** starting from methyl (4S)-6-(bromomethyl)-4-(4-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **96a** (50 mg) and **109a** (22 mg). 15 mg of the title compound was isolated as yellow powder.

Examples 114 and 115:

2-[(1R,3S,5S)-8-[[[(4S)-4-(3,4-difluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid

and 2-[(1S,3R,5R)-8-[[[(4S)-4-(3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid



Preparation of Examples 114 and 115:

Example **114** was prepared in analogy to Example **86** starting from **86j** (22 mg) and methyl (4S)-6-(bromomethyl)-4-(3,4-difluorophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **114a** (50 mg). 6 mg of Example **114** was isolated.

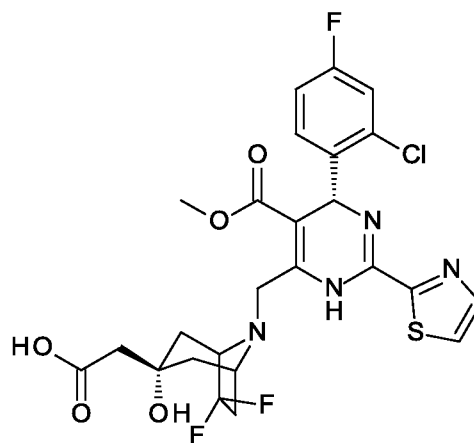
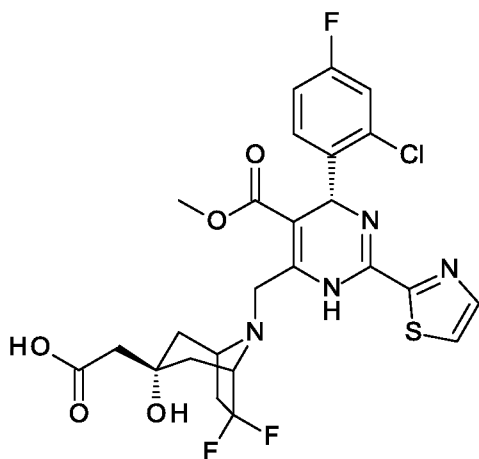
Methyl (4S)-6-(bromomethyl)-4-(3,4-difluorophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **114a** was prepared in analogy to compound **C** with procedures shown in Example **1** by using 3,4-difluoro-benzaldehyde instead of and 2-chloro-4-fluoro-benzaldehyde.

- 5 Example **115** was prepared in analogy to Example **86** starting from **86k** (22 mg) and methyl (4S)-6-(bromomethyl)-4-(3,4-difluorophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **114a** (50 mg). 8 mg of Example **115** was isolated.

Examples 116 and 117:

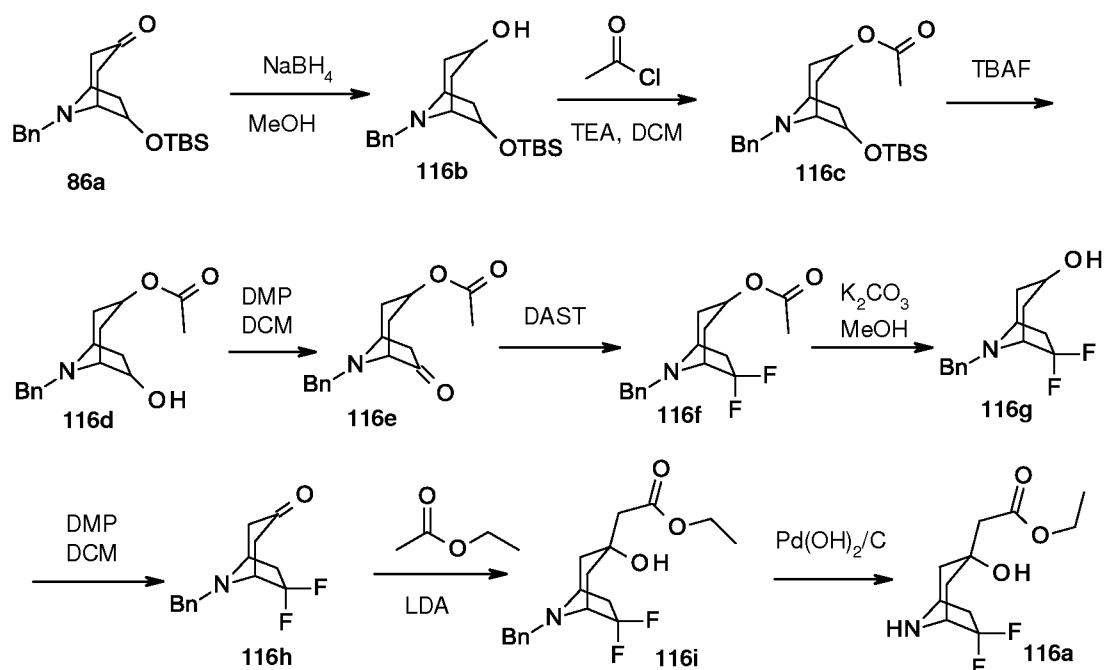
- 10 2-[(3R)-8-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid

- 15 and 2-[(3S)-8-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid



- 20 The title compounds were prepared in analogy to Example **86** starting from (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(bromomethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 225 mg) and ethyl 2-(6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl)acetate **116a** (120 mg). The crude product was purified by preparative HPLC first, and then chiral SFC, to afford Example **116** and Example **117**.

Ethyl 2-(6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl)acetate 116a:



Step I: To a solution of compound **86a** (6.9 g, 20 mmol, 1.0 eq) in MeOH (100 mL) was added NaBH₄ (1.5 g, 40 mmol, 2.0 eq) slowly at room temperature, then the mixture was stirred at room temperature for 1 h. The mixture was quenched with water (100 mL), extracted with EA (100 mL) two times. The organic layer was combined, dried over Na₂SO₄ and concentrated to give 8-benzyl-6-[tert-butyl(dimethyl)silyl]oxy-8-azabicyclo[3.2.1]octan-3-ol **116b** as a colorless oil, 6.24 g, yield: 90 %. MS: calc'd (MH⁺) 348, measured (MH⁺) 348.

Step II: A mixture of compound **116b** (6.24 g, 18 mmol, 1.0 eq) and TEA (9.2 g, 9 mmol, 5.0 eq) in DCM (100 mL) was added AcCl (4.2 g, 54 mmol) slowly and then stirred at room temperature for 2 h. The mixture was quenched with water (100 mL), extracted with DCM (100 mL), the organic layer was combined, dried over Na₂SO₄ and concentrated to give [8-benzyl-6-[tert-butyl(dimethyl)silyl]oxy-8-azabicyclo[3.2.1]octan-3-yl] acetate **116c** as a colorless oil, 6.66 g, yield: 95 %. MS: calc'd (MH⁺) 390, measured (MH⁺) 390.

Step III: A solution of compound **116c** (6.24 g, 16 mmol, 1.0 eq) and TBAF (6.26 g, 24 mmol, 1.5 eq) in THF (100 mL) was stirred at 70 °C for 20 h. The mixture was diluted with EA (100 mL), and washed with water (100 mL) two times. The organic layer was extracted with 1N HCl (100 mL), the aqueous layer was adjust to PH= 8 with NaHCO₃, extracted with DCM (100 mL) two times, the DCM layer was dried over Na₂SO₄ and concentrated to give (8-benzyl-6-hydroxy-8-azabicyclo[3.2.1]octan-3-yl) acetate **116d** as a colorless oil, 4.4 g, crude yield: 100%. MS: calc'd (MH⁺) 276, measured (MH⁺) 276.

Step IV: To a mixture of compound **116d** (4.4 g, 16 mmol, 1.0 eq) in DCM (50 mL) was added DMP (13.6 g, 32 mmol, 2.0 eq) slowly at 0 °C, then the mixture was stirred at room

temperature for 16 h. The reaction mixture was quenched with water, the solid was filtered off, the filtrate was diluted with DCM (100 mL), washed with NaHCO₃ (100 mL) three times and brine (100 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel (EA/PE= 1: 3) to give (8-benzyl-6-oxo-8-azabicyclo[3.2.1]octan-3-yl) acetate **116e** as a colorless oil. 2.2 g, two step yield: 50%. MS: calc'd (MH⁺) 274, measured (MH⁺) 274.

Step V: A mixture of ketone **116e** (2.2 g, 8 mmol, 1.0 eq) and DAST (6.44 g, 40 mmol, 5.0 eq) in DCM (15 mL) was stirred at 60°C in sealed tube for 18 h. The mixture was added dropwise to a cooled aqueous NaHCO₃ (50 mL, 5%) solution, then the mixture was extracted with EA (50 mL) two times, the organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel (EA/PE= 1: 3) to give (8-benzyl-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl) acetate **116f** as a slight yellow oil. 1.48 g, yield: 50%. MS: calc'd (MH⁺) 296, measured (MH⁺) 296.

Step VI: A solution of compound **116f** (1.48 g, 4 mmol, 1.0 eq) and K₂CO₃ (1.1 g, 8 mmol, 2.0 eq) in MeOH (20 mL) was stirred at room temperature for 16 h. The mixture was quenched with water (100 mL), extracted with EA (100 mL) two times, the organic layer was combined, dried over Na₂SO₄ and concentrated to give 8-benzyl-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-ol **116g** as a colorless oil, 1.02 g, crude yield: 100 %. MS: calc'd (MH⁺) 254, measured (MH⁺) 254.

Step VII: To a mixture of compound **116g** (1.02 g, 4 mmol, 1.0 eq) in DCM (20 mL) was added DMP (3.4 g, 8 mmol, 2.0 eq) slowly at 0 °C, then the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water, the solid was filtered off, the filtrate was diluted with DCM (100 mL), washed with NaHCO₃ (100 mL) three times and brine (100 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel (EA/PE= 1: 4) to give 8-benzyl-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-one **116h** as a colorless oil. 0.5 g. MS: calc'd (MH⁺) 252, measured (MH⁺) 252.

Step VIII: To a solution of diisopropylamine (1.02 g, 10 mmol, 5.0 eq) in THF (10 mL) was added n-BuLi (5 mL, 2.0 M, 5.0 eq) dropwise at -50 °C. After 30 min, dry EA (880 mg, 10 mmol, 5.0 eq) in NMP/THF (11 mL, 1: 10) was added dropwise. After 1 h at -50 °C, a solution of compound **116h** (500 mg, 2 mmol, 1.0 eq) in THF (5 mL) was added slowly, and the resulting mixture was warmed from -50 °C to room temperature for 2 h. The reaction mixture was quenched with water (50 mL), extracted with EA (100 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel (EA/PE= 1: 3) to give ethyl 2-(8-benzyl-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl)acetate **116i** as a colorless oil.

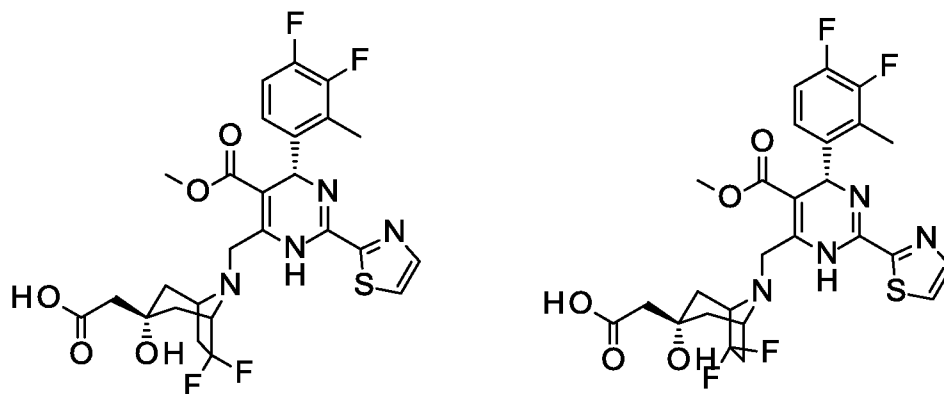
490 mg, yield: 72%. ¹H NMR (400MHz, DMSO-d₆) ppm 7.37 - 7.19 (m, 5H), 4.45 (s, 1H), 4.09 (q, J = 7.0 Hz, 2H), 3.84 - 3.70 (m, 2H), 3.27 (d, J = 5.0 Hz, 1H), 3.08 (d, J = 11.3 Hz, 1H), 2.70 (q, J = 13.6 Hz, 1H), 2.43 (s, 2H), 2.37 - 2.26 (m, 1H), 2.13 - 2.00 (m, 2H), 1.84 - 1.72 (m, 1H), 1.52 (d, J = 14.3 Hz, 1H), 1.22 (t, J = 7.0 Hz, 3H); MS: calc'd (MH⁺) 340, measured (MH⁺) 340.

Step VIII: A mixture of compound **116i** (340 mg, 1 mmol, 1.0 eq) and Pd(OH)₂/C (100 mg, 30%) in MeOH (20 mL) was stirred at room temperature for 16 h under 1 atmosphere of hydrogen. The mixture was filtered, and the filtrate was concentrated to give ethyl 2-(6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl)acetate **116a** as a colorless oil, 224 mg, yield: 90%. MS: calc'd (MH⁺) 250, measured (MH⁺) 250.

Examples 118 and 119:

2-[(3R)-8-[[4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid

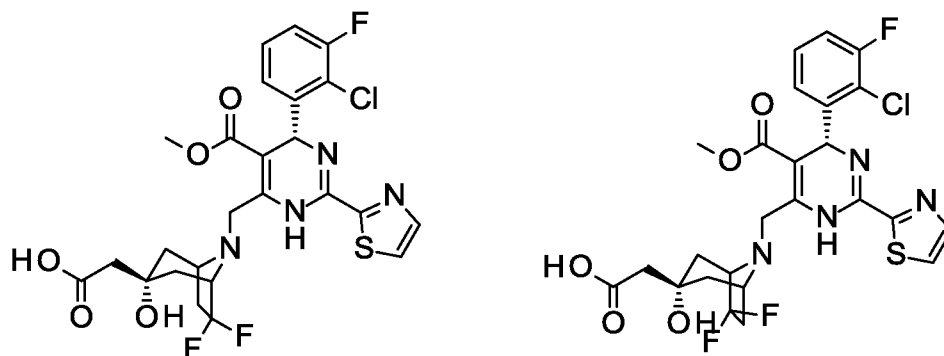
and 2-[(3S)-8-[[4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid



The title compounds were prepared in analogy to Example **86** starting from methyl (4S)-6-(bromomethyl)-4-(3,4-difluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **111a** (220 mg) and ethyl 2-(6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl)acetate **116a** (120 mg). The crude product was purified by preparative HPLC first, and then chiral SFC, to give Example **118** (20 mg) and Example **119** (15 mg).

Examples 120 and 121:

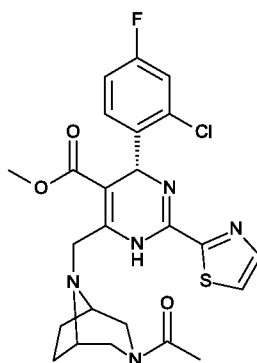
2-[(3R)-8-[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid and 2-[(3S)-8-[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid



The title compounds were prepared in analogy to Example **86** starting from methyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **88a** (220 mg) and ethyl 2-(6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl)acetate **116a** (120 mg). The crude product was purified by preparative HPLC first, and then chiral SFC, to give Example **120** (30 mg) and Example **121** (30 mg).

Example 122

Methyl (4R)-6-[(3-acetyl-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate



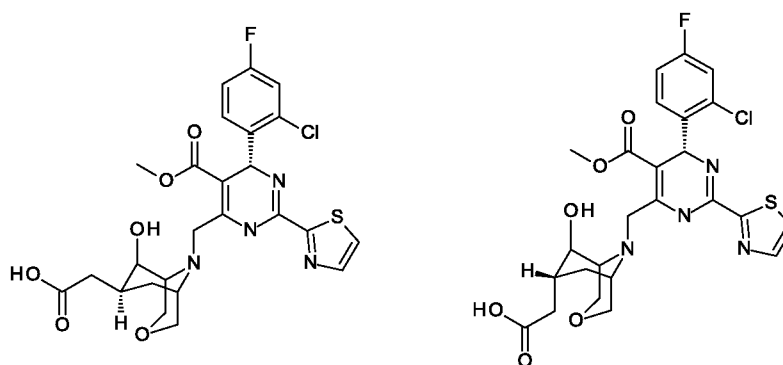
To a solution of methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 80 mg, 0.13 mmol) in dimethylformamide (3.0 mL) was added compound tert-butyl 3,8-diazabicyclo[3.2.1]octane-3-

carboxylate (28 mg, 0.13 mmol) and potassium carbonate (40 mg, 0.29 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into ice-water, extracted with EA (20 mL) three times. The combined organic phase was concentrated to give a crude tert-butyl 8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (80 mg).

A mixture of tert-butyl 8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (80 mg), trifluoroacetic acid (1.0 mL) and dichloromethane (2.0 mL) was stirred at room temperature for one hour, and then concentrated. The residue was dissolved in dichloromethane (5.0 mL), followed by adding diisopropylethylamine (0.2 mL) and acetic chloride (0.1 mL). The result mixture was stirred at room temperature overnight. The reaction mixture was concentrated and purified by prep-HPLC to give Methyl (4R)-6-[(3-acetyl-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **122** (11.3 mg).

Examples 123 and 124

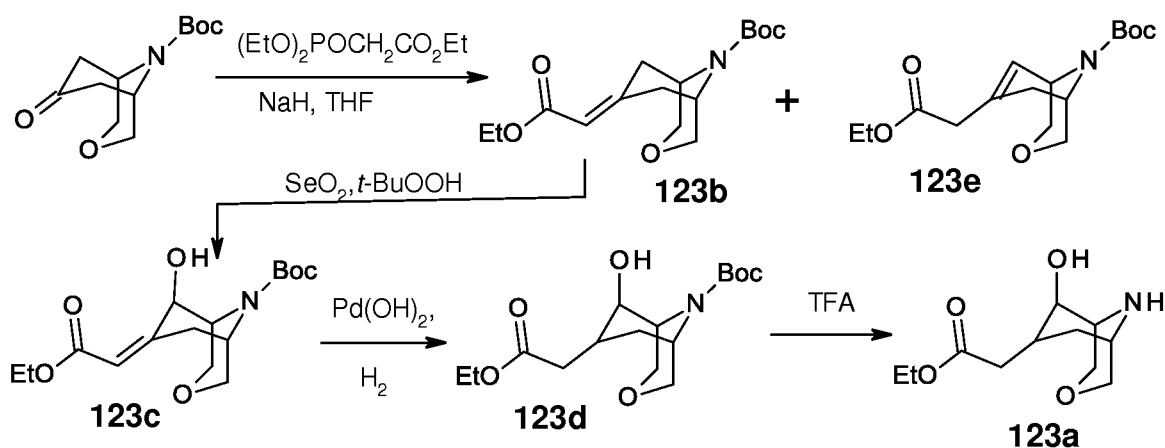
2-[(7S)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid and 2-[(7R)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid



The title compounds were prepared in analogy to Example 1 with ethyl 2-(6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **123a** and methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound C). The crude product from the final step was purified by preparative HPLC to give two compounds, Example **123**, and Example **124**.

Preparation of ethyl 2-(6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate 123a:

-208-



Step I: To a suspension of sodium hydride (396 mg, 60% dispersion in mineral oil, 9.9 mmol) in dry THF (5 ml) was added 2-diethoxyphosphorylacetic acid ethyl ester (2.40 g, 10.8 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 10 mins, and then heated at 80 °C for 20 mins. The reaction mixture was cooled down to room temperature. To the reaction mixture was added a solution of tert-butyl 7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (2.00 g, 8.3 mmol) in dry THF (20 ml). The resulting mixture was stirred at 80 °C overnight. The solvent was removed and the residue was partitioned between ethyl acetate and water. The organic phase was dried, concentrated and purified by silica gel chromatography to give tert-butyl 7-(2-ethoxy-2-oxo-ethylidene)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **123b** (1.20 g, 46.5%) and tert-butyl 7-(2-ethoxy-2-oxo-ethyl)-3-oxa-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate **123e** (0.800 g, 30.8%). Compound **123b**: ^1H NMR (400MHz, CDCl_3): δ = 5.72 - 5.66 (m, 1H), 4.29 - 4.23 (m, 1H), 4.15 (d, J = 7.3 Hz, 3H), 4.05 - 3.97 (m, 1H), 3.88 - 3.77 (m, 2H), 3.76 - 3.65 (m, 2H), 2.77 - 2.61 (m, 1H), 2.38 (d, J = 15.3 Hz, 2H), 1.53 - 1.48 (m, 9H), 1.30 - 1.26 (m, 3H).

Step II: To a solution of tert-butyl hydroperoxide in 1, 2-dichloroethane (8.0 mL, v/v 1 : 5, pre-dried over Na_2SO_4) was added compound **123b** (600 mg, 2.0 mmol) and selenium dioxide (220 mg, 2.0 mmol). The reaction mixture was sealed and heated to 70 °C under microwave for one hour. The reaction mixture was cooled down to room temperature, washed with saturated Na_2SO_3 solution, and extracted with DCM (30 mL) three times. The organic phases were combined and dried over Na_2SO_4 . After filtration and concentration, the residue was purified by silica gel column to give tert-butyl (7E/Z)-7-(2-ethoxy-2-oxo-ethylidene)-6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **123c** (563 mg, yield: 90%). ^1H NMR (400MHz, CDCl_3): δ = 5.83 - 5.44 (m, 1H), 4.36 - 4.08 (m, 5H), 3.93 - 3.55 (m, 5H), 3.13 - 3.05 (m, 0.5H), 2.82 -

2.74 (m, 0.5H), 2.30 - 2.22 (m, 0.5H), 2.10 - 2.03 (m, 0.5H), 1.53 - 1.49 (m, 9H), 1.30 - 1.26 (m, 3H).

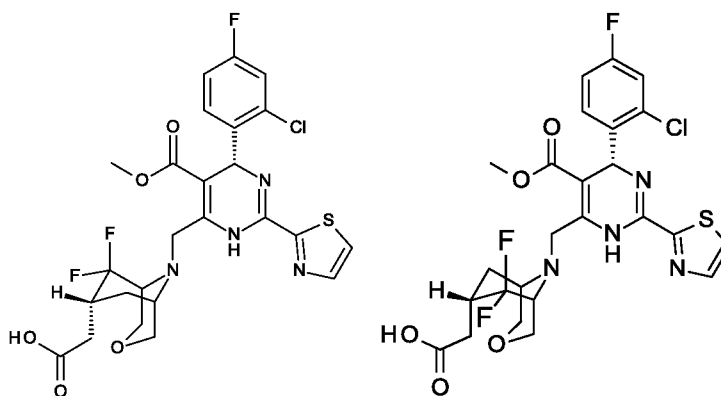
Step III: To a solution of compound **123c** (18 g, 55 mmol) in ethanol (200 mL) was added palladium hydroxide (3.0 g). The reaction mixture was stirred at 40 °C overnight under 1 atm H₂.

5 The reaction mixture was filtrated and concentrated to give tert-butyl 7-(2-ethoxy-2-oxo-ethyl)-6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **123d** (18 g, crude). ¹H NMR (400MHz, CDCl₃): d = 4.24 - 3.98 (m, 4H), 3.90 - 3.78 (m, 1H), 3.70 - 3.48 (m, 4H), 2.79 (dd, J = 5.3, 15.6 Hz, 0.5H), 2.59 (d, J = 7.0 Hz, 0.5H), 2.41 (dd, J = 5.5, 15.8 Hz, 0.5H), 2.30 (dd, J = 8.2, 15.7 Hz, 0.5H), 2.25 - 2.16 (m, 1H), 1.77 - 1.64 (m, 1H), 1.54 - 1.50 (m, 9H), 1.42 - 1.26 (m, 10 5H).

Step IV: To a solution of compound **123d** (100 mg) in dichloromethane (2.0 mL) was added trifluoroacetic acid (1.0 mL). The reaction mixture was stirred at room temperature for one hour, and concentrated under reduced pressure to give ethyl 2-(6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **123a**, which was used directly in next step without 15 purification.

Examples 125 and 126

20 **2-[(7R)-9-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid**
and 2-[(7S)-9-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid



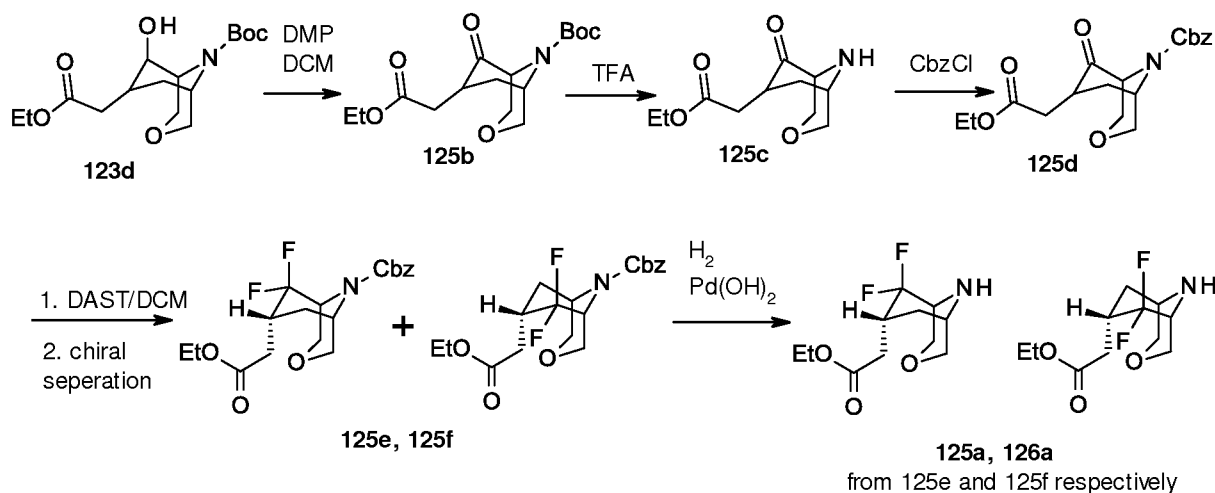
25 Preparation of Examples 125 and 126:

Example **125** was prepared in analogy to Example **86** starting from methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-

carboxylate (compound **C**) and **125a** (one of the two enantiomers of ethyl 2-endo-[6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetate).

Example **126** was prepared in analogy to Example **86** starting from methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**) and **126a** (the other enantiomer of ethyl 2-endo-[6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetate).

Preparation of the two enantiomers of ethyl 2-endo-[6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetate, **125a** and **126a**:



Step I: To a solution of compound **123d** (960 mg, 3.0 mmol) in dichloromethane (30 mL) was added Dess-Martin reagent (2.54 g, 6.0 mmol) at 40 °C. The reaction mixture was stirred for three hours, then another batch of Dess-Martin reagent (1.27 g, 3.0 mmol) was added. The reaction mixture was stirred overnight. The reaction mixture was poured into ice-water, and filtered. The filtrate was washed with sodium bicarbonate solution and sodium sulphite solution, extracted with dichloromethane (50 mL) three times. The organic phase was dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column to give tert-butyl 7-(2-ethoxy-2-oxo-ethyl)-6-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **125b** (780 mg, yield: 80%).

Step II and III: a mixture of tert-butyl 7-(2-ethoxy-2-oxo-ethyl)-6-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **125b** (654 mg, 2.0 mmol), trifluoroacetic acid (1.0 mL) and dichloromethane (2.0 mL) was stirred at room temperature for one hour. The reaction mixture was concentrated. The residue was dissolved in dimethylformamide (5.0 mL), followed by adding potassium carbonate (700 mg, 5.0 mmol) and N,N-diisopropylethylamine (0.3 mL). The result mixture was warmed to 40 °C, then added dropwise benzyl chloroformate (311 μL, 2.2 mmol) in dimethylformamide (1.0 mL). The resulting mixture was stirred for another two hours. The reaction was quenched by adding ice-water, extracted with PE : EA=5 : 1 (30 mL)

three times. The combined organic phases were dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column to give benzyl 7-(2-ethoxy-2-oxo-ethyl)-6-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **125d** (650 mg, yield: 90%).

Step IV: To a solution of benzyl 7-(2-ethoxy-2-oxo-ethyl)-6-oxo-3-oxa-9-

5 azabicyclo[3.3.1]nonane-9-carboxylate **125d** (14.4 g, 40 mmol) in dichloromethane (84 mL) was added diethylaminosulfur trifluoride (42 mL, 320 mmol). The reaction mixture was stirred at 65 °C overnight. The reaction mixture was cooled down and diluted with ethyl acetate (300 mL). The mixture was poured into ice-water and sodium bicarbonate solution at 0 °C. The reaction mixture was extracted with PE : EA=5 : 1 (150 mL) three times. The combined organic phases
10 were dried over Na₂SO₄, filtrated and concentrated. The residue was purified by silica gel column (18%EA in petroleum ether), preparative HPLC, and then chiral SFC (OJ-H, 30*250mm, 5 um, 5% isopropanol) to give a pair of enantiomers of benzyl 7-endo-(2-ethoxy-2-oxo-ethyl)-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate, **125e** (2.0 g, peak 1) and **125f** (3g, peak 2).

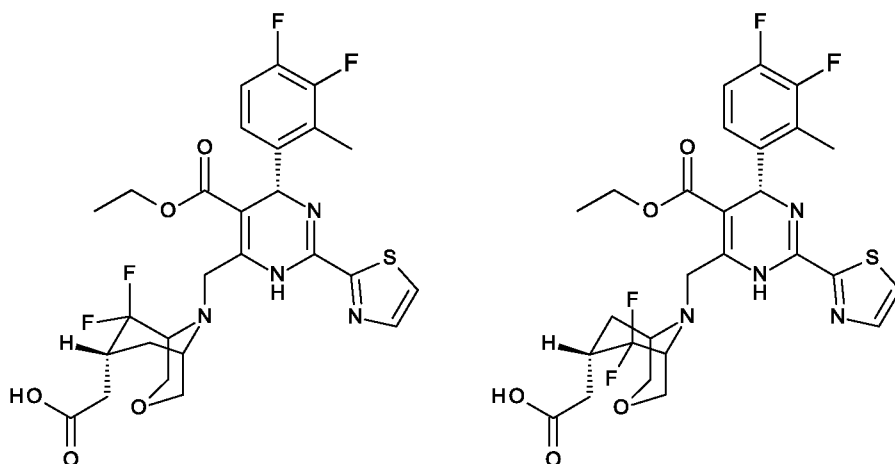
15 **Step V:** To a solution of **125e** (2.0 g, 5.22 mmol) in ethanol (25 mL) was added palladium hydroxide (1.0 g). The reaction mixture was stirred at room temperature overnight, and then diluted with ethyl acetate (300 mL). The mixture was filtrated and concentrated to give **125a**, one of the two enantiomers of ethyl 2-endo-[6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetate (1.0 g, crude).

20 The other enantiomer of ethyl 2-endo-[6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetate, **126a**, was prepared from **125f** in analogy to compound **125a**.

Examples 127 and 128:

25 2-[(7R)-9-[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid and

2-[(7S)-9-[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid



Preparation of Examples 127 and 128:

Example **127** was prepared in analogy to Example **86** starting from ethyl (4S)-6-(bromomethyl)-4-(3,4-difluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **127a** and **125a**. Compound **127a** was prepared in analogy to methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**) in Example **1**, by using ethyl acetoacetate and 3,4-difluoro-2-methyl-benzaldehyde instead of methyl acetoacetate and 2-chloro-4-fluoro-benzaldehyde, respectively.

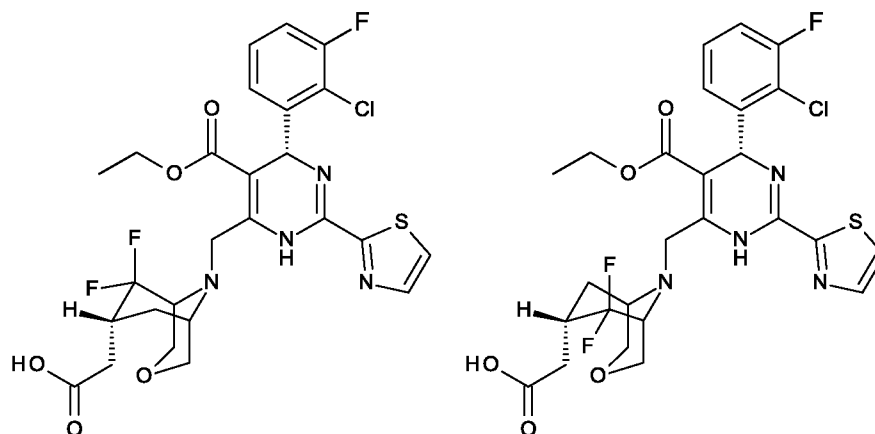
Example **128** was prepared in analogy to Example **86** starting from ethyl (4S)-6-(bromomethyl)-4-(3,4-difluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **127a** and **126a**.

Examples 129 and 130:

2-[(7R)-9-[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid and

2-[(7S)-9-[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

-213-



Preparation of Examples 129 and 130:

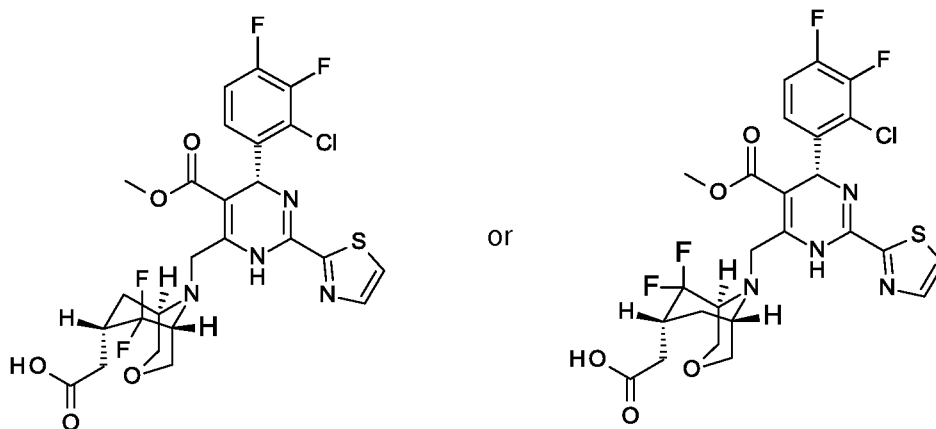
Example **129** was prepared in analogy to Example **86** starting from ethyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **98a** and **125a**.

Example **130** was prepared in analogy to Example **86** starting from ethyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **98a** and **126a**.

Example 131:

2-[(1R,5R,7S)-9-[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

or 2-[(1S,5S,7R)-9-[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid



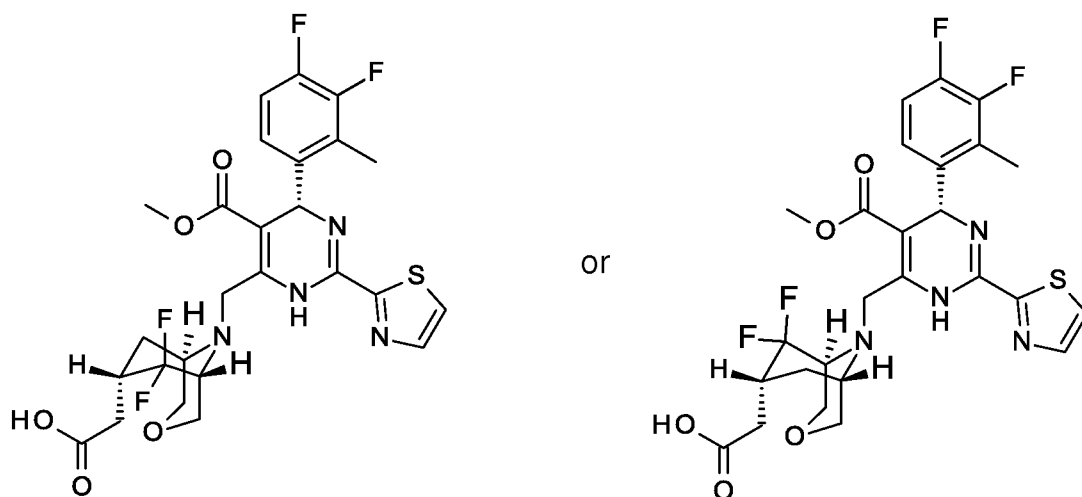
The title compound was prepared in analogy to Example **86** starting from methyl (4R)-6-(bromomethyl)-4-(2-chloro-3,4-difluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **131a** and **126a**.

Methyl (4R)-6-(bromomethyl)-4-(2-chloro-3,4-difluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **131a** was prepared in analogy to methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**) in Example **1**, by using 2-chloro-3,4-difluoro-benzaldehyde instead of 2-chloro-4-fluoro-benzaldehyde.

Example 132:

2-[(1R,5R,7S)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

or 2-[(1S,5S,7R)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

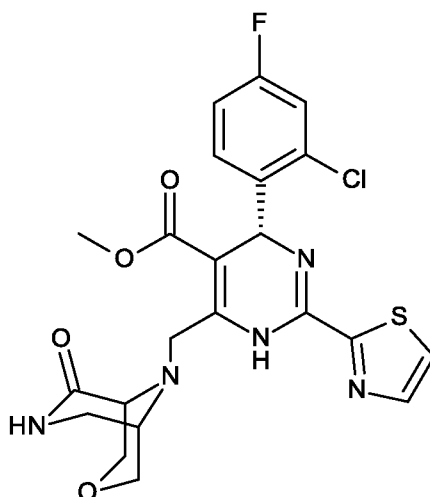


The title compound was prepared in analogy to Example **86** starting from methyl (4S)-6-(bromomethyl)-4-(3,4-difluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **111a** and **126a**.

Example 133:

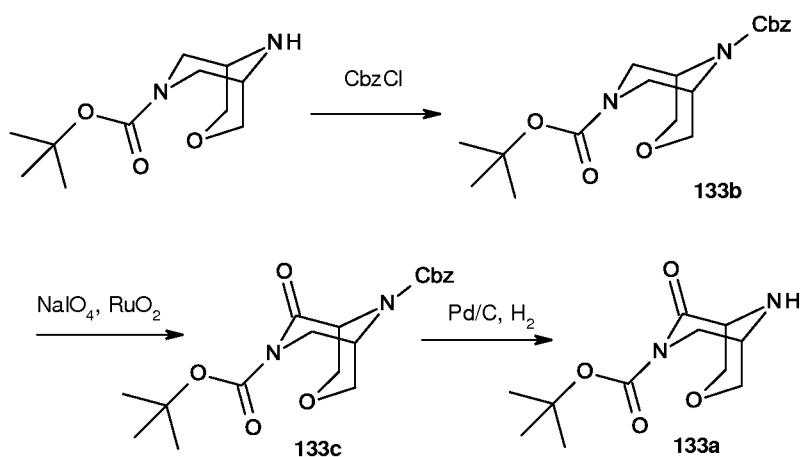
Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate

-215-



The titled compound was prepared by following procedure. To a solution of methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 0.089 g, 0.20 mmol) and tert-butyl 6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylate **133a** (0.096 g) in CH₂Cl₂ (3 ml) was added DIPEA (0.2 ml, 1.14 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was concentrated, and the residue (0.120 g, MS: calc'd (MH⁺) 606, measured (MH⁺) 606) was dissolved in dichloromethane (3 ml). To it was added trifluoroacetic acid (2 ml) at room temperature. The resulting mixture was stirred at room temperature for 2 hours. Then the mixture was concentrated and the residue was purified by preparative HPLC to give the title compound (10 mg).

Preparation of tert-butyl 6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylate **133a:**



Step I: To a solution of tert-butyl 3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylate (0.500 g, 2.2 mmol) in dichloromethane (5 ml) was added triethylamine (0.443 g, 4.4 mmol) at room temperature. The mixture was stirred at room temperature for a few mins, and then benzyl

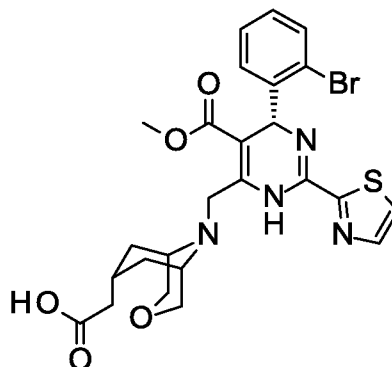
chloroformate (0.751 g, 4.4 mmol) was added to the reaction mixture. The resulting mixture was stirred at room temperature overnight. The mixture was partitioned between dichloromethane and water. The organic phase was dried, and concentrated. The residue was purified by silica gel chromatography to give 9-benzyl 7-tert-butyl 3-oxa-7,9-diazabicyclo[3.3.1]nonane-7,9-dicarboxylate **133b** (0.637 g, 80.0%). MS: calc'd (MH⁺) 363, measured (MH⁺) 363.

Step II: A solution of **133b** (0.100 g, 0.28 mmol) in ethyl acetate (1 ml) was added to a mixture of 10% NaIO₄ aqueous solution (0.283 mg in 3 ml H₂O) and RuO₂. The mixture was stirred at room temperature overnight. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (10 ml) two times. The combined organic phases were treated with isopropyl alcohol (2 ml) to decompose RuO₄ oxidant, then washed three times with H₂O (5 ml), dried, and concentrated. The crude product 9-benzyl-7-tert-butyl 6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7,9-dicarboxylate **133c** (0.150 g) was used directly in next step. MS: calc'd (MH⁺) 377, measured (MH⁺) 377.

Step III: A mixture of **133c** (150 mg, 0.40 mmol) and Pd/C (20 mg) in MeOH (5 ml) was stirred under H₂ balloon at room temperature overnight. The reaction mixture was filtered and the filtrate was concentrated to give crude tert-butyl 6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylate **133a** (96 mg), which was used directly in next step. MS: calc'd (MH⁺) 243, measured (MH⁺) 243.

Example 134:

Endo-2-[9-[[[(4R)-4-(2-bromophenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid



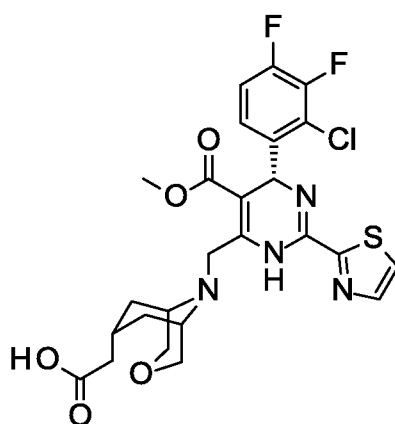
To a stirred solution of (4R)-6-(bromomethyl)-4-(2-bromophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **134a** (122 mg) and endo-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PBN20121752, 72 mg) in CH₂Cl₂ (3 ml)

-217-

was added DIPEA (0.20 ml, 1.14 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. Then the reaction mixture was concentrated and the residue was purified by prep-HPLC to give the title compound (23 mg). (4R)-6-(bromomethyl)-4-(2-bromophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **134a** was prepared in analogy to compound **C** in Example **1** by using 2-bromoaldehyde instead of 2-chloro-4-fluorobenzaldehyde.

Example 135:

Endo-2-[9-[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

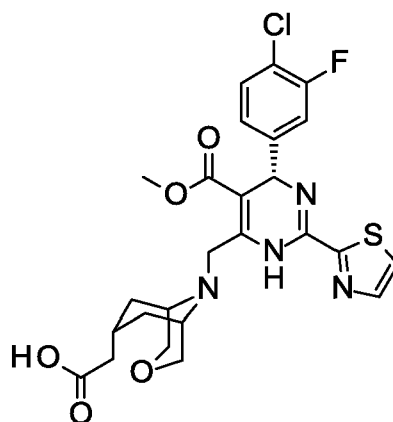


The title compound was prepared in analogy to Example 134, starting from methyl (4R)-6-(bromomethyl)-4-(2-chloro-3,4-difluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **131a** (200 mg) and endo-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid (PharmaBlock (Nanjing) R&D Co. Ltd , PBN20121752, 120 mg). 115 mg of the title compound was isolated.

Example 136:

Endo-2-[9-[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid

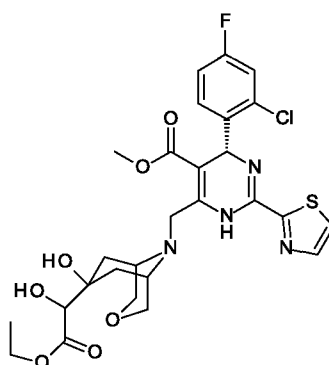
-218-



The title compound was prepared in analogy to Example **134**, starting from methyl (4S)-6-(bromomethyl)-4-(4-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **96a** (50 mg) and endo-(3-oxa-9-aza-bicyclo[3.3.1]non-7-yl)-acetic acid
 5 (PharmaBlock (Nanjing) R&D Co. Ltd , PBN20121752, 40 mg). 10 mg of the title compound was isolated.

Example 137

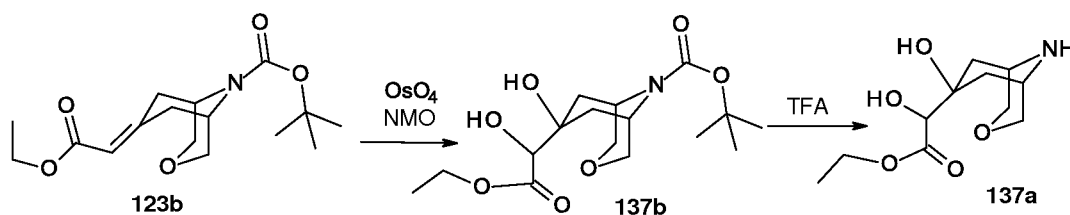
Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-1-hydroxy-2-oxo-ethyl)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate



The title compound was prepared in analogy to Example **134**, starting from methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 58 mg) and ethyl 2-hydroxy-2-(7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **137a** (96 mg). 7 mg of the title compound was isolated.

Preparation of 2-hydroxy-2-(7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate 137a:

-219-

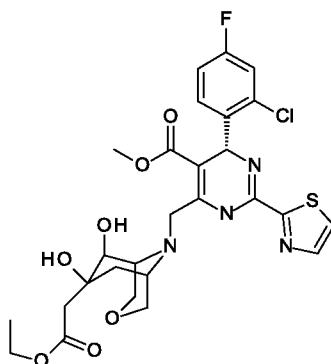


Step I: To a mixture of tert-butyl 7-(2-ethoxy-2-oxo-ethylidene)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate **123b** (0.800 g, 2.6 mmol) in acetone (8 ml) and water (2 ml) were added N-methylmorpholine-N-oxide (0.903 g, 7.7 mmol) and Osmium tetroxide solution (0.3 ml, 4 wt % in H₂O, 1.2 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was then concentrated and the crude diol **137b** (0.950 g) was used directly in next step without further purification.

Step II: To a solution of diol **137b** (150 mg, 0.43 mmol) in dichloromethane (2 ml) was added trifluoroacetic acid (2 ml) at room temperature. The resulting mixture was stirred at room temperature for 2 hours, then concentrated to give 2-hydroxy-2-(7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **137a** (120 mg) as a crude product, which was used directly in next step.

Example 138

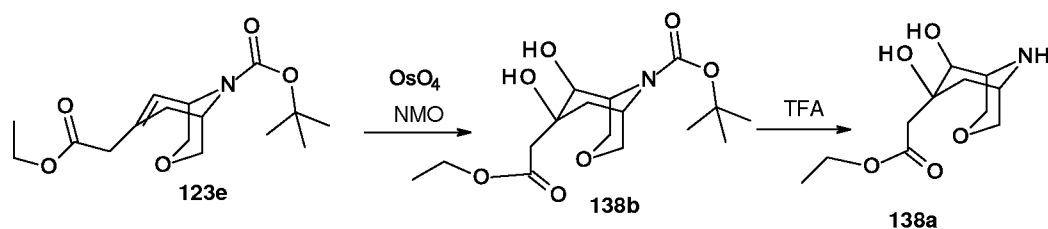
Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-6,7-dihydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate



The title compound was prepared in analogy to Example 134, starting from methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 86 mg) and ethyl 2-(6,7-dihydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **138a** (142 mg). 6 mg of the title compound was isolated.

Preparation of ethyl 2-(6,7-dihydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **138a**:

-220-

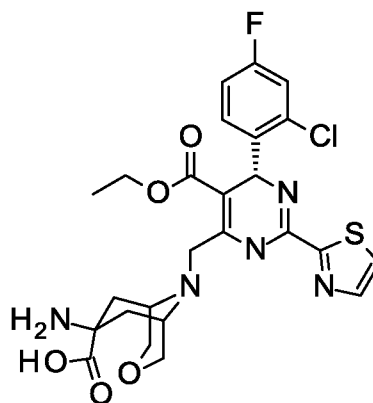


Step I: To a tert-butyl 7-(2-ethoxy-2-oxo-ethyl)-3-oxa-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate **123e** (0.800 g, 2.6 mmol) in acetone (8 ml) and water (2 ml) were added N-methylmorpholine-N-oxide (0.903 g, 7.7 mmol) and Osmium tetroxide solution (0.3 ml, 4 wt % in H₂O, 1.2 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was then concentrated to give crude diol **138b** (0.900 g), which was used directly in next step without further purification. MS: calc'd (MH⁺) 346, measured (MH⁺) 346.

Step II: To a solution of diol **138b** (200 mg, 0.58 mmol) in dichloromethane (2 ml) was added trifluoroacetic acid (2 ml) at room temperature. The resulting mixture was stirred at room temperature for 2 hours, then concentrated to give 142 mg of ethyl 2-(6,7-dihydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **138a**, which was used directly in next step. MS: calc'd (MH⁺) 246, measured (MH⁺) 246.

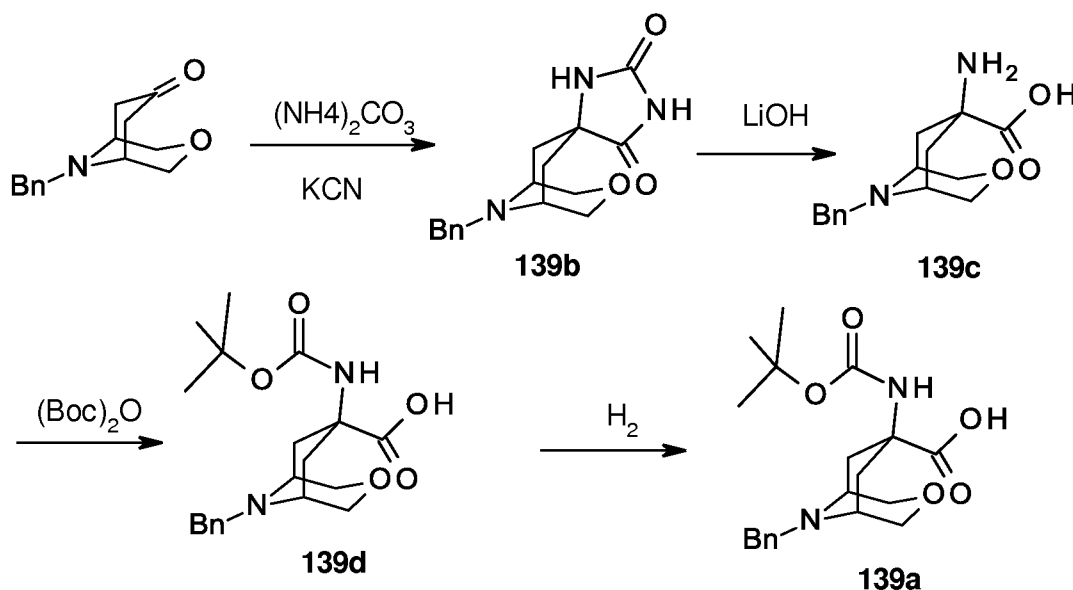
Example 139:

7-amino-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid



The title compound was prepared in analogy to Example **133** by using 7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid **139a** (40 mg) and methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 39 mg). 4 mg of the title compound was isolated.

Preparation of 7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid **139a**:



Step I: A mixture of 9-benzyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one (0.9 g, 3.9 mmol),
 5 KCN (760 mg, 11.7 mmol), and $(\text{NH}_4)_2\text{CO}_3$ (1.1 g, 11.7 mmol) in EtOH (8 ml) and H_2O (8 ml)
 was stirred at 55°C for 2 days. Then the mixture was poured into water (100 ml) and extracted
 with DCM (100 ml) two times. The organic layer was dried and concentrated to obtain a residue.
 The residue was purified by chromatography on silica gel (PE/EA=1:1 then DCM/MeOH=15:1)
 to give 9-benzylspiro[3-oxa-9-azabicyclo[3.3.1]nonane-7,5'-imidazolidine]-2',4'-dione **139b** (0.6
 10 g, 70%) as white solid. MS: calc'd (MH^+) 302, measured (MH^+) 302.

Step II: LiOH (240 mg, 10 mmol) was added to a suspension of compound **139b** (0.3 g, 1
 mmol) in H_2O (30 ml). The resulting mixture was stirred at 100°C for 40 h. The mixture was cooled
 to room temperature and filtered to remove a white solid, and the filtrate was evaporated. The pH
 of the concentrate was adjusted from 12 to 5 with concentrated HCl, and the solution was
 15 evaporated to dryness. The residue was treated with methanol to lead to a suspension. After
 filtration and being washed with CH_3OH , the solid was dried to give 7-amino-9-benzyl-3-oxa-9-
 azabicyclo[3.3.1]nonane-7-carboxylic acid **139c** (200 mg, 72%) as white solid. MS: calc'd
 (MH^+) 277, measured (MH^+) 277.

Step III: NaOH (45 mg, 1.1 mmol) was added to a mixture of compound **139c** (100 mg,
 20 0.36 mmol) and $(\text{Boc})_2\text{O}$ (457 mg, 0.72 mmol) in THF (15 ml) and H_2O (15 ml). The mixture
 was stirred at 70°C overnight. The THF was evaporated and the water solution was acidified
 with 1N HCl until pH=5. The water solution was extracted with EA (3x50 ml). The organic layer
 was dried and concentrated to give a residue. The residue was purified by pre-HPLC to afford 9-

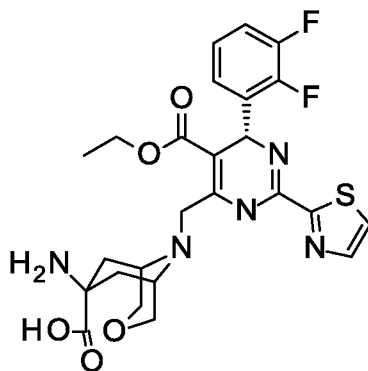
benzyl-7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid **139d** (50 mg, 37%) as white solid. MS: calc'd (MH⁺) 377, measured (MH⁺) 377; ¹HNMR (400 MHz, CDCl₃) δ 1.45 (s, 9H), 2.30-2.33 (m, 2H), 2.50-2.55 (m, 2H), 3.02-3.04 (d, 2H), 3.69-3.72 (d, 2H), 4.12-4.22 (m, 4H), 7.35-7.41 (m, 3H), 7.47-7.49 (d, 2H).

- 5 **Step IV:** A mixture of compound **139d** (0.050 g, 0.13 mmol) and Pd/C (20 mg) in MeOH (5 ml) was stirred under H₂ balloon at room temperature overnight. The mixture was filtered and the filtrate was concentrated to give 40 mg of the crude 7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid **139a**, which was used directly in next step without further purification. MS: calc'd (MH⁺) 287, measured (MH⁺) 287.

10

Example 140:

7-amino-9-[[[(4R)-4-(2,3-difluorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid



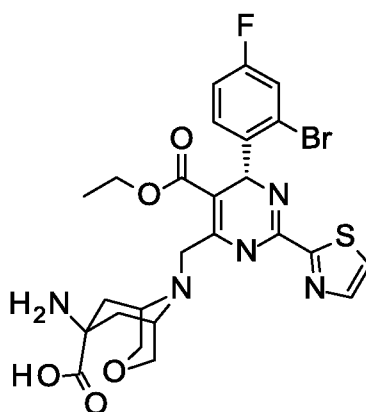
- 15 The title compound was prepared in analogy to Example **133** by using 7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid **139a** (49 mg) and ethyl (4R)-6-(bromomethyl)-4-(2,3-difluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **140a** (48 mg). 5 mg of the title compound was isolated.

- 20 Ethyl (4R)-6-(bromomethyl)-4-(2,3-difluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **140a** was prepared in analogy to compound **C** in Example **1** by using ethyl acetoacetate and 2,3-difluorobenzaldehyde instead of methyl acetoacetate and 2-chloro-4-fluoro-benzaldehyde, respectively.

Example 141:

- 25 **7-amino-9-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid**

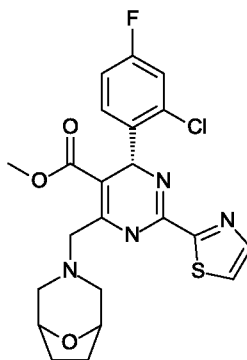
-223-



The title compound was prepared in analogy to Example **133** by using 7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid **139a** (49 mg) and ethyl (4R)-6-(bromomethyl)-4-(2-bromo-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **70a** (55 mg). 15 mg of the title compound was isolated.

Example 142:

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(8-oxa-3-azabicyclo[3.2.1]octan-3-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate

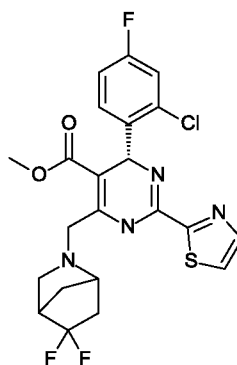


The title compound was prepared in analogy to Example **1a** in Example **1** by using methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 200 mg) and 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (100mg). 44 mg of title compound was isolated.

Example 143:

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate

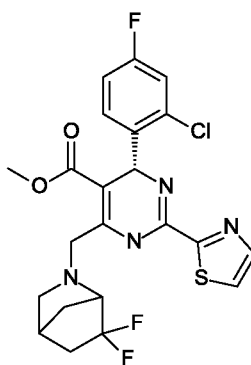
-224-



The title compound was prepared in analogy to Example **1a** in Example **1** by using methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 50 mg) and 5,5-difluoro-2-azabicyclo[2.2.1]heptane (Wuxi AppTec Co., Ltd, WX120101, 29 mg). 7 mg of title compound was isolated.

Example 144:

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(5,5-difluoro-3-azabicyclo[2.2.1]heptan-3-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate

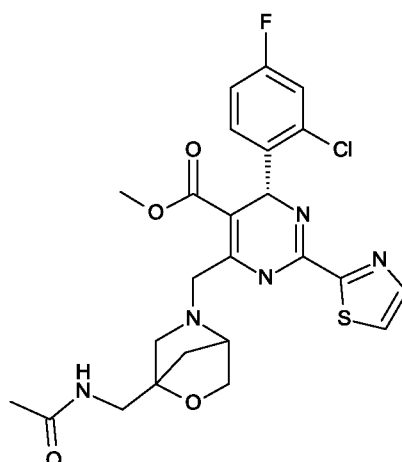


The title compound was prepared in analogy to Example **1a** in Example **1** by using methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 50 mg) and 5,5-difluoro-3-azabicyclo[2.2.1]heptane (Wuxi AppTec Co. Ltd, WX120379, 29 mg). 26 mg of title compound was isolated.

Example 145:

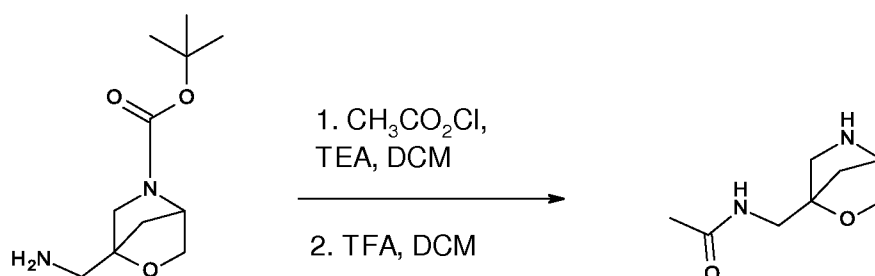
Methyl (4R)-6-[[4-(acetamidomethyl)-5-oxa-2-azabicyclo[2.2.1]heptan-2-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate

-225-



The title compound was prepared in analogy to Example 1a in Example 1 by using methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound C, 65 mg) and N-(5-oxa-2-azabicyclo[2.2.1]heptan-4-ylmethyl)acetamide (37 mg). 5.5 mg of title compound was isolated.

Preparation of N-(5-oxa-2-azabicyclo[2.2.1]heptan-4-ylmethyl)acetamide:

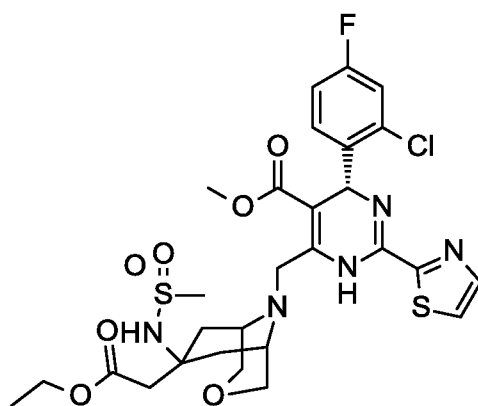


A mixture of tert-butyl 4-(aminomethyl)-5-oxa-2-azabicyclo[2.2.1]heptane-2-carboxylate (Wuxi AppTec, CAS 1357351-98-4) (50 mg, 0.22 mmol), TEA (44.4 mg, 0.44 mmol) in DCM (2 mL) was added CH₃CO₂Cl (26 mg, 0.33 mmol) at 0°C. After 2 hours, the solvent was removed under reduced pressure. The residue was treated with TFA in DCM. After stirring for 2 hours at room temperature, the residue was used in next step without purification. MS: calc'd (MH⁺) 271, measured (MH⁺) 271.

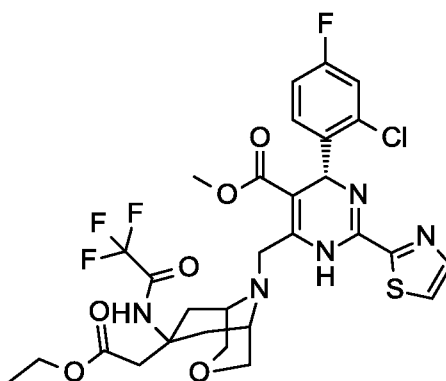
Examples 146 and 147:

Example 146: Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-7-(methanesulfonamido)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate

-226-

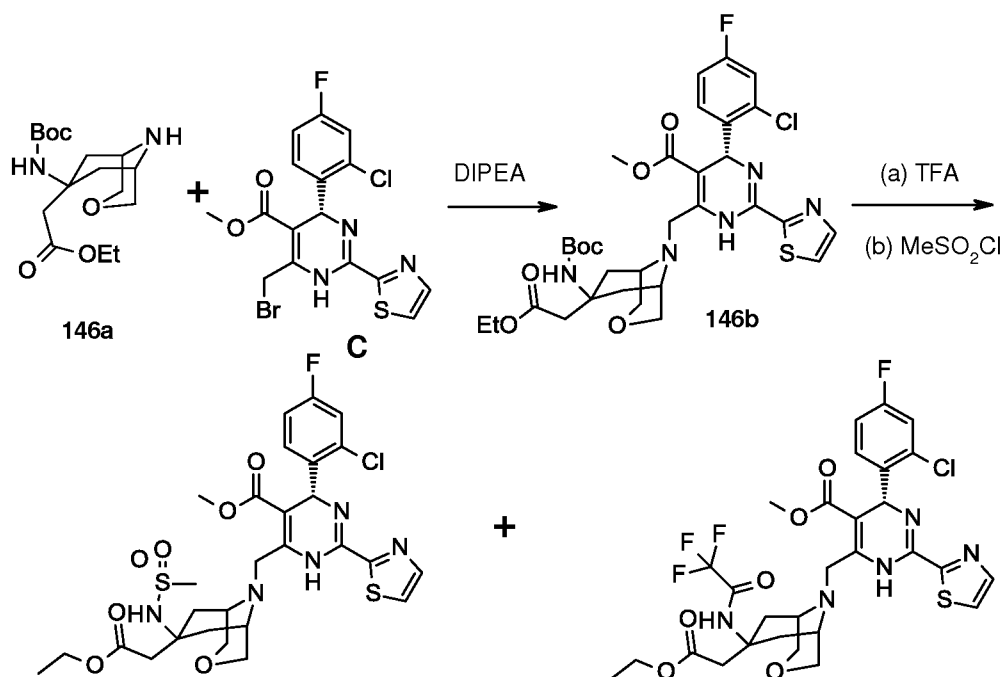


Example 147: Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-7-[(2,2,2-trifluoroacetyl)amino]-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate



5

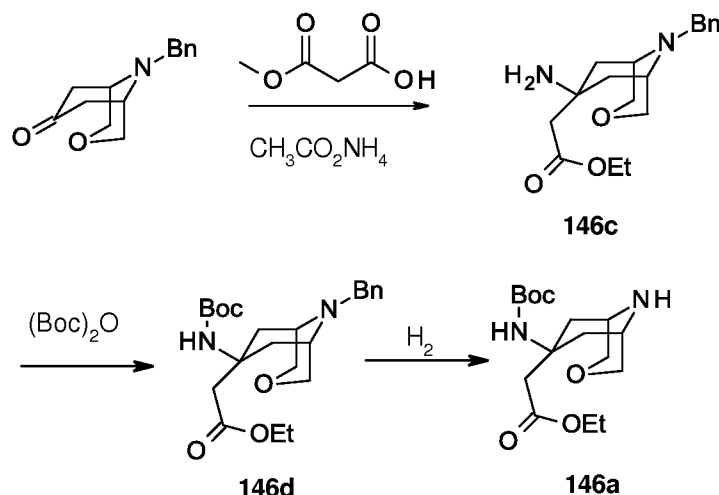
Preparation of Example 146 and Example 147:



A mixture of ethyl 2-[7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetate **146a** (0.1g, 0.3mmol) and methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **C** (90 mg, 0.2 mmol), DIPEA (77.4 mg, 0.6mmol) in DCM (5mL) was stirred for 12 hours at room temperature. The mixture was concentrated to give crude methyl (4R)-6-[[7-(tert-butoxycarbonylamino)-7-(2-ethoxy-2-oxo-ethyl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **146b**. MS: calc'd (MH⁺) 692, exp (MH⁺) 692.

A mixture of **146b** (0.14 g, 0.20 mmol), TFA (2 mL) in DCM (5 mL) was stirred for 2 hours. The solvents were removed under reduced pressure to give crude methyl (4R)-6-[[7-amino-7-(2-ethoxy-2-oxo-ethyl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate in TFA salt form. MS: calc'd (MH⁺) 592, exp (MH⁺) 592. This TFA salt (35mg, 0.051 mmol) was dissolved in a mixture of TEA (20.6 mg, 0.204 mmol) in DCM (3 mL). To it was added CH₃SO₂Cl (11.7 mg, 0.102mmol). The resulting mixture was stirred for 12 hours at room temperature, and concentrated under reduced pressure. The residue was purified by preparative HPLC to give two products, Example **146** and Example **147**.

Preparation of ethyl 2-[7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetate **146a:**



Step I: The mixture of 9-benzyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one (0.5g, 2.2mmol), 3-methoxy-3-oxopropanoic acid (0.44g, 3.3 mmol), ammonium acetate (0.33g, 4.4 mmol) in ethanol (5 mL) was refluxed for 3 hours. After removal of solvent, the residue was purified by flash silica gel chromatography to afford ethyl 2-(7-amino-9-benzyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate **146c**. Yield: 5%. MS: calc'd (MH⁺) 319, measured (MH⁺)

319.

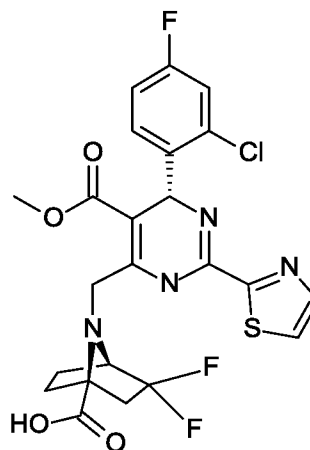
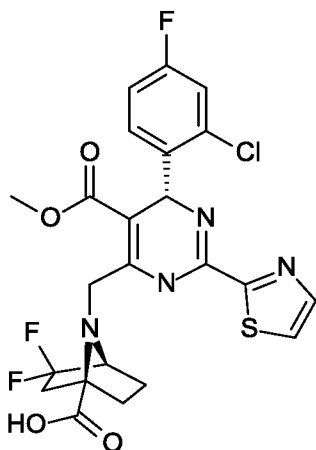
Step II: A mixture of ethyl 2-(7-amino-9-benzyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)acetate (1.2 g, 3.8mmol), (Boc)₂O (1.23g, 5.7mmol), and TEA(0.77g, 7.6mmol) in DCM (15 mL) was stirred for 2 hours at room temperature. After removal of solvent, the residue was purified by flash silica gel chromatography to afford ethyl 2-[9-benzyl-7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetate **146d** as an oil, 1.5g, yield, 95%. MS: calc'd (MH⁺) 419, measured (MH⁺) 419.

Step III: A mixture of ethyl 2-[9-benzyl-7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetate (0.7g, 1.67 mmol), 10% Pd/C (0.5g) in methanol (20 mL) was stirred for 12 hours under 1 atm H₂. Filtration followed by removal of the residue gave ethyl 2-[7-(tert-butoxycarbonylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetate **146a**, which was used in next step without purification. Yield: 96%. MS: calc'd (MH⁺) 329, measured (MH⁺) 329.

Examples 148 and 149

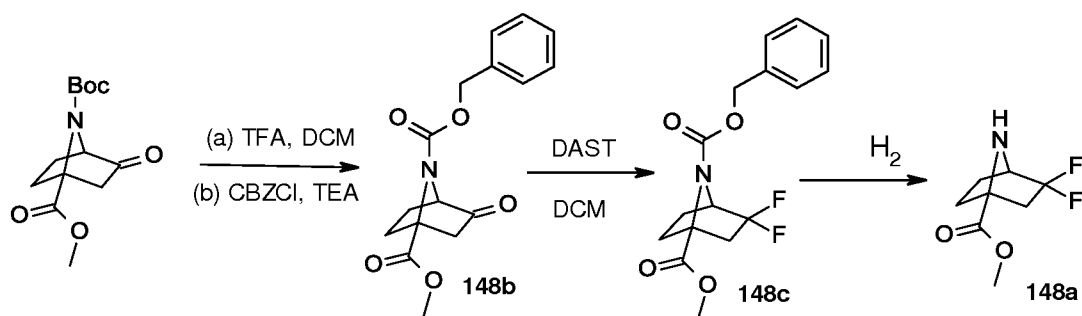
(1S,4R)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylic acid and

(1R,4S)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylic acid



The title compounds were prepared in analogy to Example 1 by using methyl 2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylate **148a** (22 mg) and methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound **C**, 106 mg). Final purification by preparative HPLC afforded two products, Example 148 and example 149.

Preparation of methyl 2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylate 148a:



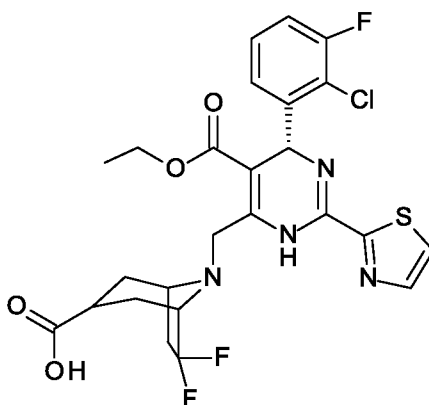
Step I: A mixture of O7-tert-butyl O4-methyl 2-oxo-7-azabicyclo[2.2.1]heptane-4,7-dicarboxylate (prepared according to the literature: Org. Lett., Vol. 9, No. 7, 2007 p1235-p1238) (0.34 g, 1.27 mmol), TFA (1.5 ml) in DCM was stirred for 2 hours. After removal of solvent and TFA under reduced pressure, the residue was dissolved into DCM (5 mL). To it was added TEA (0.51g, 5.08 mmol) and CbzCl (0.43g, 2.54 mmol). After 12 hours, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to give O7-benzyl O4-methyl 2-oxo-7-azabicyclo[2.2.1]heptane-4,7-dicarboxylate **148b**. Yield:30%. MS: calc'd (MH⁺) 304, measured (MH⁺) 304.

Step II: A mixture of O7-benzyl O4-methyl 2-oxo-7-azabicyclo[2.2.1]heptane-4,7-dicarboxylate (0.5 g, 1.65 mmol) and DAST (2.66 g, 16.5 mmol) in DCM (2 mL) was heated for 12 hours at 45 °C, then quenched with water, extracted with DCM, washed with NaHCO₃ (aq), After removal of solvent, the residue was purified by flash chromatography to give O7-benzyl O4-methyl 2,2-difluoro-7-azabicyclo[2.2.1]heptane-4,7-dicarboxylate **148c**, Yield:8%. MS: calc'd (MH⁺) 326, measured (MH⁺) 326.

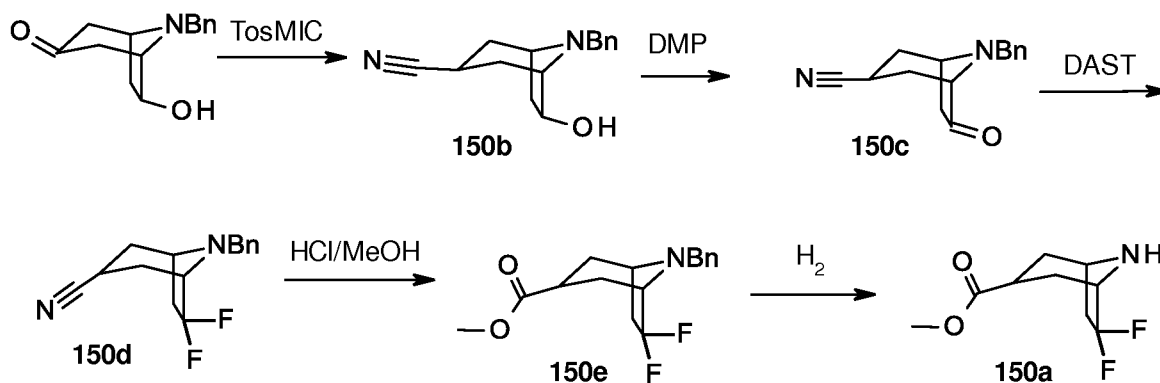
Step III: The mixture of O7-benzyl O4-methyl 2,2-difluoro-7-azabicyclo[2.2.1]heptane-4,7-dicarboxylate (0.24g, 0.74 mmol), 10% Pd/C (0.3g) in methanol (20 mL) was stirred for 12 hours under 1 atm H₂. Removal of the catalyst solid and solvent gave methyl 2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylate **148a**. This crude product was used in next step without purification. Yield: 69.3%. MS: calc'd (MH⁺) 192, measured (MH⁺) 192.

Example 150:

8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octane-3-carboxylic acid



The title compound was prepared in analogy to Example 1, by using methyl 6,6-difluoro-8-azabicyclo[3.2.1]octane-3-carboxylate **150a** (200 mg) and ethyl (4R)-6-(bromomethyl)-4-(2-chloro-3-fluorophenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate **98a** (400 mg). 30 mg of the title compound was isolated finally after preparative HPLC purification. Preparation of methyl 6,6-difluoro-8-azabicyclo[3.2.1]octane-3-carboxylate **150a**:



Step I: To a mixture of 8-benzyl-6-hydroxy-8-azabicyclo[3.2.1]octan-3-one (1.2g) and TosMIC (1.95g) in a mixture of 20 mL of DME and 0.5 mL of absolute EtOH was added t-BuOK (3.5 g) portionwise while keeping the temperature between 5 and 10°C. The resulting mixture was stirred at room temperature 30 min, and then warmed to 35-40 °C for another 30 minutes. The suspension thus obtained was cooled to room temperature, and the precipitate (TosK) was removed and extracted with DME. The combined DME solutions were concentrated to 3 mL and purified by silica gel chromatography to give 8-benzyl-6-hydroxy-8-azabicyclo[3.2.1]octane-3-carbonitrile **150b** (0.8g).

Step II: 0.8g of nitrile **150b** was dissolved in 10 ml of DCM. Then 3eq of Dess-Martin reagent was added to the solution and stirred at room temperature overnight. The mixture was filtered and the filtrate was concentrated to give 8-benzyl-6-oxo-8-azabicyclo[3.2.1]octane-3-

carbonitrile **150c** as a crude product (0.9g), which was used in the next step without further purification.

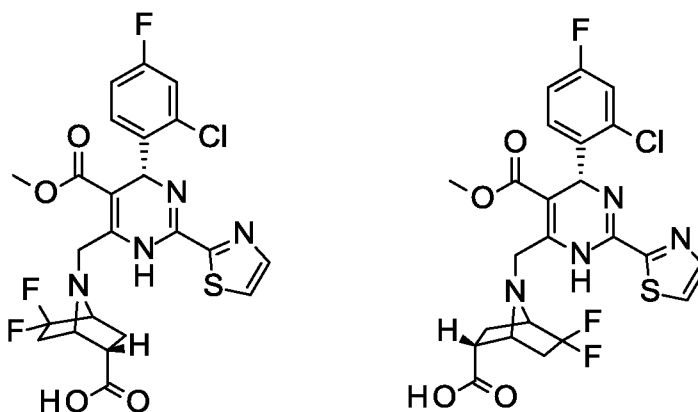
Step III: 0.3g of ketone **150c** was dissolved in 1ml of DCM. To it was added 0.5ml of DAST. The resulting mixture was heated at 60 °C overnight, then concentrated. The residue was purified by silica gel chromatography to give 0.2 g of 8-benzyl-6,6-difluoro-8-azabicyclo[3.2.1]octane-3-carbonitrile **150d** as an oil.

Step IV: 0.2 g of compound **150d** was dissolved in 10ml of 2 M HCl in methanol and heated at 80 °C overnight. After removal of the solvent, the residue was purified by silica gel chromatography to give methyl 8-benzyl-6,6-difluoro-8-azabicyclo[3.2.1]octane-3-carboxylate **150e** as an oil, 0.22g.

Step V: A mixture of compound **150d** (0.22g) and Pd(OH)₂ (25 mg) in 20 ml methanol under 1 atm of H₂ was stirred at room temperature overnight. Removal of the solvent afforded methyl 6,6-difluoro-8-azabicyclo[3.2.1]octane-3-carboxylate **150a** (200mg).

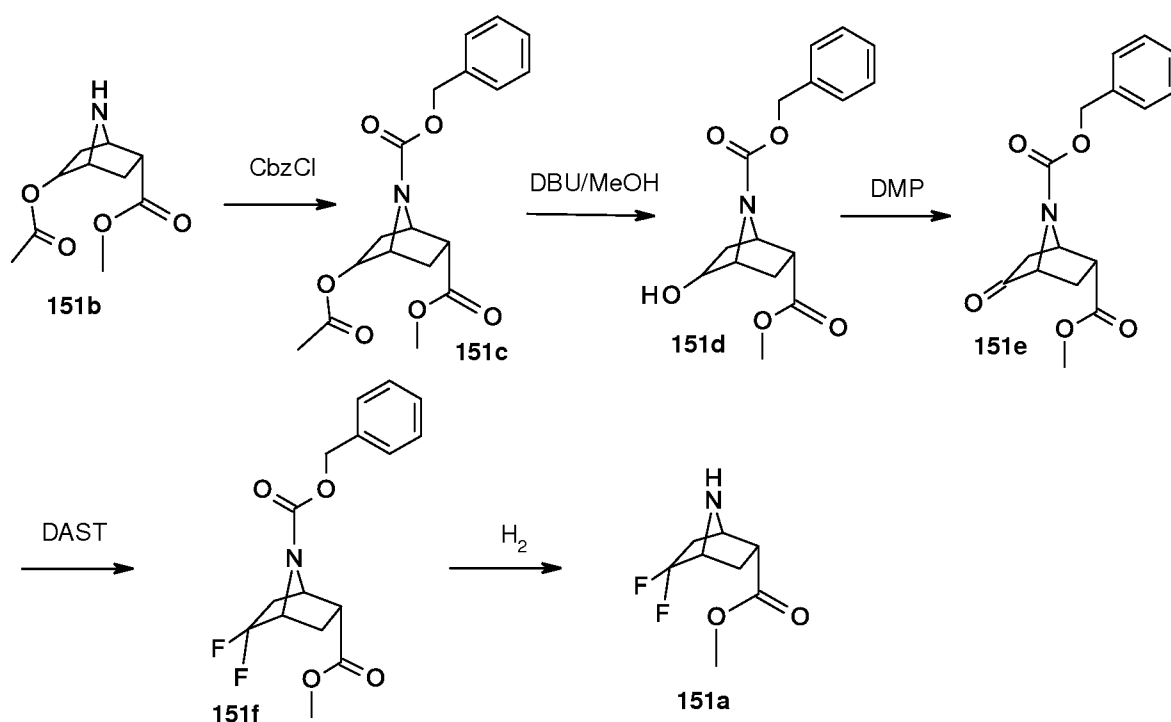
Examples 151 and 152

(5S)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-5-carboxylic acid
(5R)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-5-carboxylic acid



The title compounds were prepared in analogy to Example 1 by using methyl 2,2-difluoro-7-azabicyclo[2.2.1]heptane-5-carboxylate **151a** (150 mg) and methyl (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound C, 520 mg) in the N-alkylation step. Purification of the final product by preparative HPLC afforded Example **151** (2 mg) and Example **152** (2 mg).

Preparation of methyl 2,2-difluoro-7-azabicyclo[2.2.1]heptane-5-carboxylate 151a:



Step I: A mixture of ethyl (5R)-2-acetoxy-7-azabicyclo[2.2.1]heptane-5-carboxylate 151b (prepared in analogy to O7-tert-butyl O4-methyl 2-oxo-7-azabicyclo[2.2.1]heptane-4,7-dicarboxylate starting from methyl trans-6-acetamidocyclohex-3-ene-1-carboxylate with procedures reported in the literature: Org. Lett., Vol. 9, No. 7, 2007 p1235-p1238) (0.55g, 2.4 mmol) in DCM (10 mL) and sodium carbonate (0.76g, 7.2 mmol) in water (3 mL) was added CbzCl (0.61g, 3.6 mmol) dropwise. After addition, the mixture was stirred for 2 hours, then extracted with DCM. Removal of solvent afforded O7-benzyl O5-methyl 2-acetoxy-7-azabicyclo[2.2.1]heptane-5,7-dicarboxylate **151c**, which was used in next step without purification. Crude yield: 100%. MS: calc'd (MH⁺) 362, measured (MH⁺) 362.

Step II: A mixture of O7-benzyl O5-ethyl (5R)-2-acetoxy-7-azabicyclo[2.2.1]heptane-5,7-dicarboxylate (0.87g, 2.4 mmol) and DBU (0.73 g, 4.8 mmol) in methanol (20 mL) was stirred for 12 hours at room temperature. After removal of solvent, the residue was purified by silica gel chromatography to give O7-benzyl O5-ethyl (5R)-2-hydroxy-7-azabicyclo[2.2.1]heptane-5,7-dicarboxylate **151d**. Yield: 45%. MS: calc'd (MH⁺) 306, measured (MH⁺) 306.

Step III: A mixture of O7-benzyl O5-ethyl (5R)-2-hydroxy-7-azabicyclo[2.2.1]heptane-5,7-dicarboxylate (0.37g, 1.1 mmol), Dess-martin reagent (1.38g, 3.3 mmol) in DCM (50 mL) was stirred for 12 hours. After removal of solvent, the residue was purified by silica gel chromatography to give O7-benzyl O5-ethyl (5R)-2-oxo-7-azabicyclo[2.2.1]heptane-5,7-dicarboxylate **151e**. Yield: 90%. MS: calc'd (MH⁺) 304, measured (MH⁺) 304.

Step III: A mixture of O7-benzyl O5-ethyl (5R)-2-oxo-7-azabicyclo[2.2.1]heptane-5,7-dicarboxylate (0.4 g, 1.32 mmol), DAST (2.13g, 13.2 mmol) in DCM (2 mL) was stirred for 12 hours at 50 °C, then quenched with water, extracted with DCM. After removal of solvent, the residue was purified by silica gel chromatography to give O7-benzyl O5-ethyl (5R)-2,2-difluoro-7-azabicyclo[2.2.1]heptane-5,7-dicarboxylate **151f**. Yield: 38%. MS: calc'd (MH⁺) 326, measured (MH⁺) 326.

Step IV: A mixture of O7-benzyl O5-ethyl (5R)-2,2-difluoro-7-azabicyclo[2.2.1]heptane-5,7-dicarboxylate (0.33 g, 1.0 mmol), 10% Pd/C (0.4 g) in methanol (20 mL) was stirred for 24 hours at 1 atm of H₂. Removal of catalyst and solvent afforded crude methyl 2,2-difluoro-7-azabicyclo[2.2.1]heptane-5-carboxylate **151a**, which was used in next step without purification. Yield: 100%. MS: calc'd (MH⁺) 192, measured (MH⁺) 192.

Example 153: HBV inhibition assays

Cell lines and culture conditions:

HepG2.2.15 and HepDE19 are stably-transfected cell lines containing the HBV genome. Both cell lines are derived from the hepatoblastoma cell line Hep G2 (American Type Culture Collection, ATCC® HB-8065™) by the published procedures described in references: MA Selles et al. Proc. Natl. Acad. Sci. USA 1987, 84, 1005-1009 and H Guo et al. Journal of Virology 2007, 81, 12472-12484, respectively. Both cell lines were maintained in Dulbecco's modified Eagle's medium (DMEM)-F12 medium supplemented with 10% fetal bovine serum, 100 U/mL penicillin, 100 µg/mL streptomycin, and 0.5 mg/mL of G418.

While HepG2.2.15 cells constitutively support HBV replication and production of virus particles, HepDE19 cells are inducible by tetracycline. Addition of 1 µg/mL tetracycline in culture medium suppresses HBV replication in HepDE19 cells, whereas switching to tetracycline-free medium resumes this process.

Anti-HBV activity in vitro:

HepG2.2.15 cells were seeded into 96-well plates (3×10^4 cells in 100 µL media per well) and incubated overnight at 37 °C. The test compounds were serially half-log diluted in DMSO, then diluted 100 times in culture media. 100 µL diluted compounds were added into the plates to reach 0.5% final concentration of DMSO in every well. Five days after compound treatment, culture supernatant was collected for further analysis.

For quantitative PCR detection of extracellular HBV DNA, 100 µL culture supernatant was collected and processed in MagNA Pure 96 Nucleic Acid Purification System (Roche

Applied Science) for viral DNA extraction. The extracted samples were subjected to HBV DNA quantification by qPCR. The effective compound concentration at which HBV replication is inhibited by 50% (EC_{50}) was determined.

The Examples were tested in the above assays as described herein and found to have EC_{50} <1 μ M in HepG2.2.15 assay. Particular compounds of formula I were found to have EC_{50} <0.1 μ M in HepG2.2.15 assay (See Table 2).

Cytotoxicity and selectivity indexes:

In a cell culture model, apparent antiviral activity of a compound can be the result of host cell death after exposure to the compound. To determine whether the anti-HBV effect of a test compound is due to cytotoxicity, HepDE19 cells were seeded into 96-well plates (5×10^3 cells per well) and treated with compounds as described above for EC_{50} determination. Five days after treatment, cell viability was measured by addition of 20 μ L of CCK-8 reagent. Two hours after incubation at 37°C, the absorbance at wavelengths of 450 nm and 630 nm (OD_{450} and OD_{630}) was recorded by a plate reader. The concentration results in the death of 50% of the host cells (CC_{50}) of each compound was determined (See Table 5).

Based on CC_{50} and EC_{50} data, selectivity indexes were determined as shown in Table 5.

Example 154: Human microsomal clearance assay:

Microsomes were preincubated with test compound for 10 minutes at 37°C in 100 mM phosphate buffer with pH 7.4. The reactions were initiated by adding NADPH regenerating system to give a final incubation volume of 400 μ L. The incubations finally contained 1 μ M test compound, 0.5 mg/mL liver microsomal protein, 3.0 mM glucose 6-phosphate, 1.0 mM NADP, 3.0 mM $MgCl_2$ and 0.05 mg/mL glucose 6-phosphate dehydrogenase in 100 mM phosphate buffer with pH 7.4. After incubation times of 0, 3, 6, 9, 15 and 30 minutes, 50 μ L incubation was transferred to the quench solution containing the internal standard which was 2 μ M tolbutamide. After precipitation and centrifugation, test compound concentrations in the samples were determined by LC-MS/MS. Controls of no NADPH regenerating system at zero and 30 minutes were also prepared and analyzed.

Results of human microsomal clearance data of particular compounds are given in Table 3.

Example 155: LYSA description

Samples are prepared in duplicate from 10 mM DMSO stock solutions. After evaporation of DMSO with a centrifugal vacuum evaporator, the residue is solved in 0.05 M phosphate

buffer (pH 6.5), stirred for one hour and then shook for two hours. After one night, the solution is filtered using a microtiter filter plate and then the filtrate and its 1/10 dilution are then analyzed by direct UV measurement or by HPLC-UV. In addition a four-point calibration curve is prepared from the 10 mM stock solutions and used for the solubility determination of the compounds. The results are in $\mu\text{g/ml}$. In case the percentage of sample measured in solution after evaporation divided by the calculated maximum of sample amount is bigger than 80% the solubility is reported as bigger than this value.

Results of Lysa are given in Table 4.

Example 156: Cytochrome P450 (Cyp450) induction screening assay

MATERIALS

Cell culture

Human cryopreserved hepatocytes (Life Technologies, Carlsbad, USA) were thawed and cultured in collagen I coated 96-well plates with a density of 52,000 cells/well. After attachment, medium was changed and cells were pre-cultured overnight in hepatocyte maintenance medium (HMM; Lonza, Switzerland).

Test compounds were dosed to the cells next morning at an indicated concentration (up to 10 μM) in HMM culture media containing gentamycin and a constant 0.1 % DMSO. Similarly, dilutions of the positive inducer compounds omeprazole (prototypical inducer of human CYP1A2; final concentrations: 1 and 10 μM), phenobarbital (prototypical inducer of human CYP2B6; final concentrations: 100 and 1000 μM) and rifampicin (prototypical inducer of human CYP3A4; final concentrations: 1 and 10 μM) were prepared from 1000 fold DMSO stock solutions in HMM containing gentamycin. Medium change was then performed and cells were exposed for 24 hours to test compounds, positive inducer compounds, or vehicle (0.1 % DMSO), respectively.

At the end of the compound exposure period, medium was removed and cells lysed using 100 μL /well MagNA Pure LC RNA isolation tissue lysis buffer (Roche Diagnostics AG, Rotkreuz, Switzerland). Plates were then sealed and frozen at -80°C until further workup.

mRNA isolation, processing and qRT-PCR

mRNA isolation was performed using the MagNA Pure 96 system (Roche Diagnostics AG, Rotkreuz, Switzerland) and the respective cellular RNA large volume kit (Roche Diagnostics AG, Rotkreuz, Switzerland) from thawed samples diluted 1:1 with PBS. The volume of the cell lysis and an elution volume of 100 μL were used. 20 μL of the resulting mRNA suspension was then

used for reverse transcription using 20 µL of the transcript or first stand cDNA synthesis kit (Roche prime Supply, Mannheim, Germany). The resulting cDNA was diluted with 40 µL of H₂O before using for qRT-PCR. qRT-PCR was performed by using the forward and the reverse primer, the corresponding UPL (all from Microsynth, Balgach, Switzerland) and the Taqman

5 Fast advanced master mix (Applied Biosystems), on an ABI 7900 machine (Applied Biosystems).

Calculations

qRT-PCR Ct-values for the respective P450s were put into relation to the Ct-value of RN18S1 (microsynth, Balgach, Switzerland) of the same sample. Doing so, a respective ΔCt-value was calculated. Using the average of all ΔCt-values for the vehicle control samples, a ΔΔCt-value was calculated for each sample (ΔΔCt-value(sample) = ΔCt-value(sample) - average of ΔCt-value of all vehicle controls). The fold induction of the respective sample was calculated as 2^(-ΔΔCt). The individual fold induction values were then averaged per treatment condition (usually n=3 biological replicates).

15 Relative induction values to the respective positive inducer compound condition (10 µM omeprazole for CYP1A2; 1000 µM Phenobarbital for CYP2B6; 10 µM rifampicin for CYP3A4) were then calculated from the fold induction values as follows:

$$\text{Relative induction (\%)} = 100 \times (T - V) / (P - V)$$

T: fold induction of test compound condition

P: fold induction of positive inducer compound

20 V: fold induction of vehicle controls

Results of CYP3A4 induction are given in Table 6.

Example A

25 A compound of formula I can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	<u>Per tablet</u>
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
30 Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	<u>20 mg</u>
	425 mg

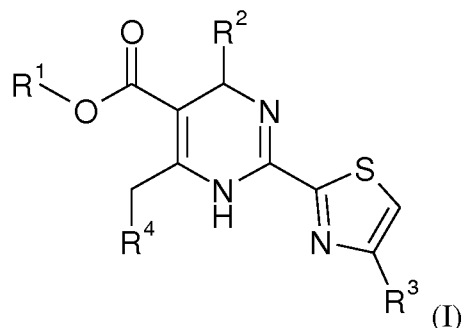
Example B

A compound of formula I can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	<u>Per capsule</u>
5 Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	<u>0.5 mg</u>
10	220.0 mg

Claims

1. A compounds of formula (I)



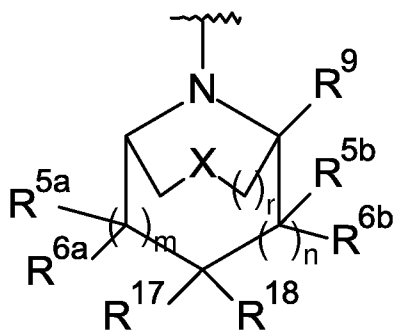
- 5 wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen or C_{1-6} alkyl;

R^3 is hydrogen or C_{1-6} alkyl;

R^4 is



wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen, halogen or hydroxy;

one of R^{5b} and R^{6b} is hydrogen or halogen, and the other one is hydrogen or halogen;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, halogen, hydroxy, amino, C_{1-6} alkylsulfonylamino or trifluoromethylcarbonylamino, the other one is hydrogen, halogen, hydroxy- $C_yH_{2y}-$, C_{1-6} alkylcarbonyl-O-, C_{1-6} alkoxycarbonyl- $C_yH_{2y}-$, carboxy- $C_yH_{2y}-O-$, carboxy- $C_yH_{2y}-$, C_{1-6} alkylcarbonyl-NH-, C_{1-6} alkylsulfonyl-NH-, aminocarbonyl-NH- or aminosulfonyl-NH-;

-239-

wherein $-C_yH_{2y}-$ is unsubstituted once or more times substituted by hydroxy;

or R^{6a} and R^{17} together with the carbon atoms, to which they are attached, form a ring of isoxazolyl, pyrazolyl or oxo-dihydropyrazolyl, which ring is unsubstituted or once or more times substituted by C_{1-6} alkyl;

or R^{17} and R^{18} together with the carbon atom, to which they are attached, form diazirinyl;

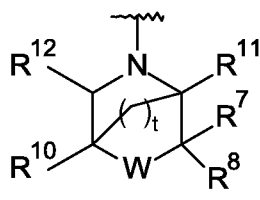
X is oxygen; sulfur; $-N(\text{carbonyl}C_{1-6}\text{alkyl})-$; or $-C(R^{15}R^{16})-$, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen or carboxy- $C_yH_{2y}-$;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

y is 0-6;



15 or R^4 is

wherein R^7 is hydrogen or halogen;

R^8 is hydrogen or halogen;

R^{10} is hydrogen, halogen, hydroxy- $C_yH_{2y}-$ or C_{1-6} alkylcarbonylamino- $C_yH_{2y}-$;

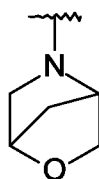
R^{11} is hydrogen or carboxy;

R^{12} is hydrogen or carboxy;

W is a bond, oxygen, $-CH_2-$, $-CF_2-$ or $-N(\text{carbonyl}C_{1-6}\text{alkyl})-$;

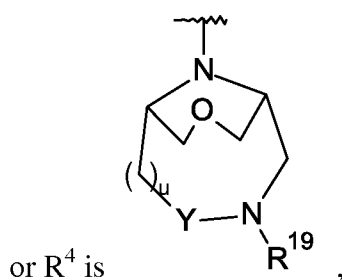
t is 1 or 2;

y is 0-6;



with the proviso that

is excluded;

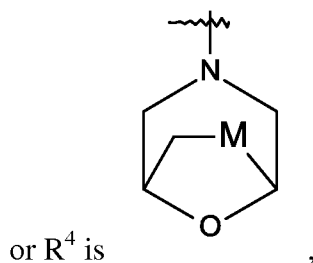


wherein R¹⁹ is hydrogen; C₁₋₆alkyl, which is unsubstituted or once or more times substituted by halogen; C₁₋₆alkoxycarbonyl-C_yH_{2y}-; hydroxy-C_yH_{2y}-carbonyl; carboxy-C_yH_{2y}-carbonyl; C₁₋₆alkylaminosulfonyl; C₁₋₆alkylcarbonyl; C₁₋₆alkylsulfonyl; aminocarbonyl; or aminosulfonyl;

Y is carbonyl or -CH₂-;

u is 0 or 1;

y is 0-6;



wherein M is a bond, -CH₂- or -N(R¹⁴)-CH₂-;

R¹⁴ is C₁₋₆alkoxycarbonyl;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

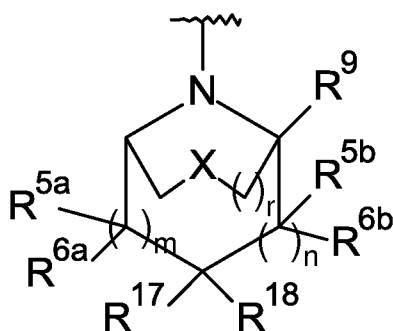
2. A compound according to claim 1, wherein

R¹ is methyl or ethyl;

R² is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

R³ is hydrogen or methyl;

R⁴ is



wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen, fluoro or hydroxy;

one of R^{5b} and R^{6b} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, fluoro, hydroxy, amino, methylsulfonylamino or trifluoromethylcarbonylamino, the other one is hydrogen, fluoro, hydroxy, hydroxymethyl, methylcarbonyl-O-, methoxycarbonyl,

methoxycarbonylmethyl, ethoxycarbonylmethyl,

methoxycarbonyl(hydroxy)methyl, ethoxycarbonyl(hydroxy)methyl,

carboxymethyl-O-, carboxy, carboxymethyl, methylcarbonylamino, aminocarbonylamino, methylsulfonylamino or aminosulfonylamino;

or R^{6a} and R^{17} together with the carbon atoms, to which they are attached, form a ring of isoxazolyl, pyrazolyl or oxo-dihydropyrazolyl, which ring is unsubstituted or once or more times substituted by methyl;

or R^{17} and R^{18} together with the carbon atom, to which they are attached, form diazirinyl;

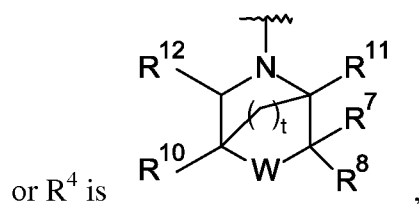
X is oxygen; sulfur; -N(carbonylmethyl)-; or -C($R^{15}R^{16}$)-, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen, carboxy or carboxymethyl;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

-242-



wherein R⁷ is hydrogen or fluoro;

R⁸ is hydrogen or fluoro;

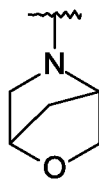
R¹⁰ is hydrogen, fluoro, hydroxymethyl or methylcarbonylaminomethyl;

R¹¹ is hydrogen or carboxy;

R¹² is hydrogen or carboxy;

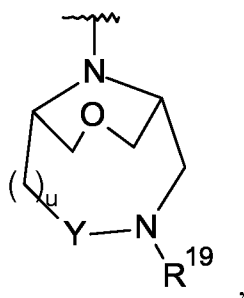
W is a bond, oxygen, -CH₂-, -CF₂- or -N(carbonylmethyl)-;

t is 1 or 2;



with the proviso that

is excluded;



wherein R¹⁹ is hydrogen, methyl, isopropyl, difluoromethylmethyl,

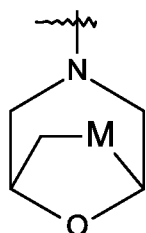
methylcarbonyl, methoxycarbonyl, ethoxycarbonylisopropyl,

hydroxymethylcarbonyl, carboxyisopropylcarbonyl, aminocarbonyl,

methylsulfonyl, aminosulfonyl or methylaminosulfonyl;

Y is carbonyl or -CH₂-;

u is 0 or 1;



or R⁴ is

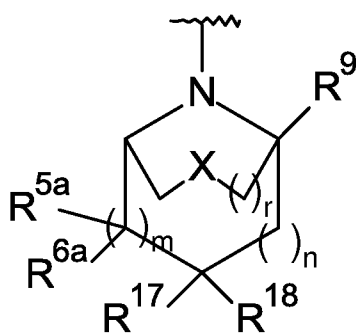
wherein M is a bond, -CH₂- or -N(carbonyltert-butoxy)-CH₂-;
or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

5 3. A compound according to claim 1, wherein

R¹ is C₁₋₆alkyl;

R² is phenyl, which is once or twice or three times substituted by halogen or C₁₋₆alkyl;

R³ is hydrogen or C₁₋₆alkyl;

 $\mathbb{R}^4$ is

wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen or halogen;

R⁹ is hydrogen or carboxy;

one of R¹⁷ and R¹⁸ is hydrogen or C₁₋₆alkylsulfonylamino, the other one is

hydrogen, C₁₋₆alkoxycarbonyl-C_yH_{2y}-, carboxy-C_yH_{2y}-O-, carboxy-C_yH_{2y}-, C₁₋₆alkylcarbonyl-NH-, C₁₋₆alkylsulfonyl-NH- or aminosulfonyl-NH-;

or R^{6a} and R¹⁷ together with the carbon atoms, to which they are attached, form pyrazolyl;

X is oxygen; sulfur; or $-C(R^{15}R^{16})-$, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen or carboxy- $C_yH_{2y}-$;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

y is 0-6;

25 or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

4. A compound according to claim 1 or 3, wherein

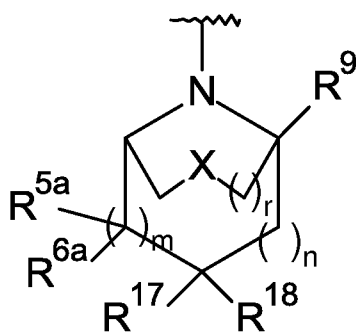
-244-

R^1 is methyl or ethyl;

R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

R^3 is hydrogen or methyl;

5 R^4 is



wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

R^9 is hydrogen or carboxy;

10 one of R^{17} and R^{18} is hydrogen or methylsulfonylamino, the other one is hydrogen, ethoxycarbonylmethyl, carboxymethyl-O-, carboxy, carboxymethyl, methylcarbonyl-NH-, methylsulfonyl-NH- or aminosulfonyl-NH-; or R^{6a} and R^{17} together with the carbon atoms, to which they are attached, form pyrazolyl;

15 X is oxygen; sulfur; or $-C(R^{15}R^{16})-$, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen, carboxy or carboxymethyl;

r is 0 or 1;

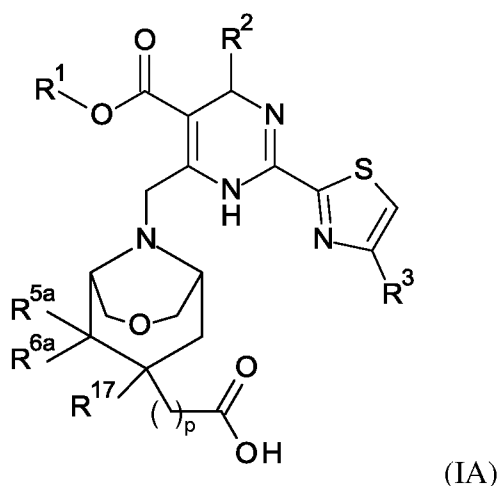
m is 0 or 1;

n is 0 or 1;

20 or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

5. A compound of formula (IA) according to claim 1,

-245-



(IA)

wherein

R¹ is C₁₋₆alkyl;

R² is phenyl, which is once or twice or three times substituted by halogen or C₁₋₆alkyl;

5 R³ is hydrogen or C₁₋₆alkyl;

one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen, halogen or hydroxy;

R¹⁷ is hydrogen or amino;

p is 0 or 1;

10 or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

6. A compound according to claim 1 or 5, wherein

R¹ is methyl or ethyl;

15 R² is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

R³ is hydrogen or methyl;

one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen, fluoro or hydroxy;

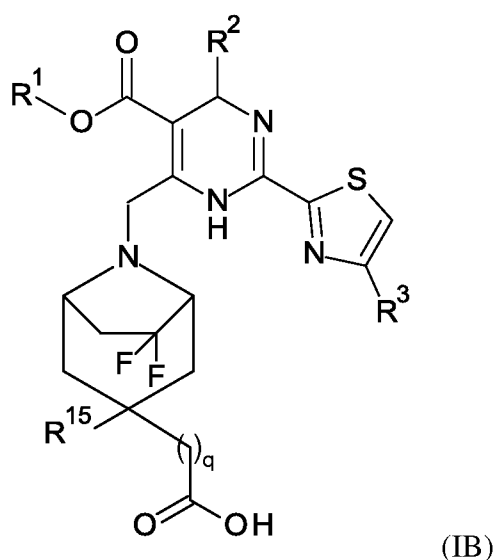
R¹⁷ is hydrogen or amino;

20 p is 0 or 1;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

7. A compound of formula (IB) according to claim 1,

-246-



wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen or C_{1-6} alkyl;

5 R^3 is hydrogen;

R^{15} is hydrogen or hydroxy;

q is 0 or 1;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

10

8. A compound according to claim 1 or 7, wherein

R^1 is methyl or ethyl;

R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro, bromo or methyl;

15 R^3 is hydrogen;

R^{15} is hydrogen or hydroxy;

q is 0 or 1;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

20

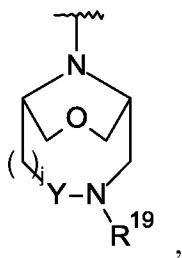
9. A compound according to claim 1, wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen;

R^3 is hydrogen;

-247-

R⁴ is

wherein R¹⁹ is hydrogen, aminocarbonyl, aminosulfonyl or hydroxy-C_yH_{2y}-carbonyl;

5 Y is -CH₂- or carbonyl;

j is 0 or 1;

y is 0-6;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

10

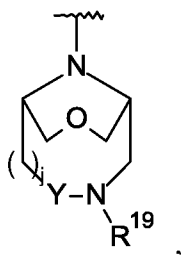
10. A compound according to claim 1 or 9, wherein

R¹ is methyl;

R² is phenyl, which is once or twice or three times substituted by fluoro or chloro;

R³ is hydrogen;

15 R⁴ is



wherein R¹⁹ is hydrogen, aminocarbonyl, aminosulfonyl or hydroxymethylcarbonyl;

Y is -CH₂- or carbonyl;

20 j is 0 or 1;

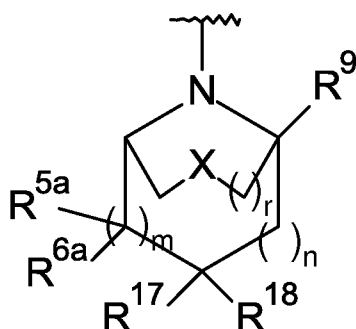
or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

11. A compound of formula I, wherein

25 R¹ is C₁₋₆alkyl;

R² is phenyl, which is once or twice or three times substituted by halogen;

R³ is hydrogen;

 $\mathbb{R}^4$ is

5 wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen or halogen;
R⁹ is hydrogen or carboxy;
one of R¹⁷ and R¹⁸ is hydrogen, the other one is hydrogen or carboxy-C_yH_{2y}-;
X is oxygen; or -C(R¹⁵R¹⁶)-, wherein one of R¹⁵ and R¹⁶ is hydrogen or
10 hydroxy, and the other one is hydrogen or carboxy-C_yH_{2y}-;
r is 0 or 1;
m is 1;
n is 0 or 1;
y is 0-6;
15 or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof.

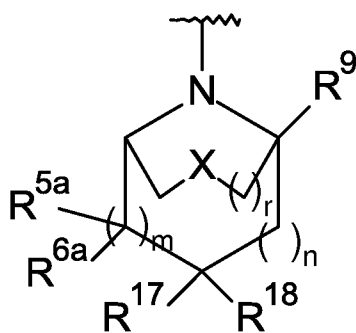
12. A compound of formula I, wherein

R¹ is methyl or ethyl;

20 R^2 is phenyl, which is once or twice or three times substituted by fluoro or chloro;

R³ is hydrogen;

 $\mathbb{R}^4$ is



wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, the other one is hydrogen or carboxymethyl;

X is oxygen; or $-C(R^{15}R^{16})-$, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen or carboxymethyl;

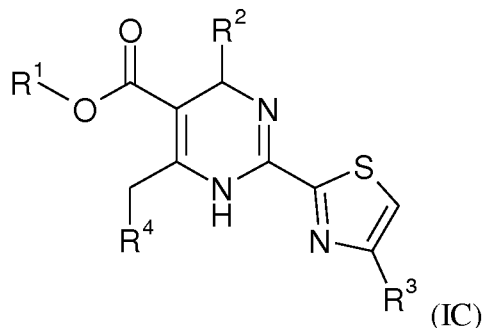
r is 0 or 1;

m is 1;

n is 0 or 1;

or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof.

13. Compounds of formula (IC) according to claim 1,



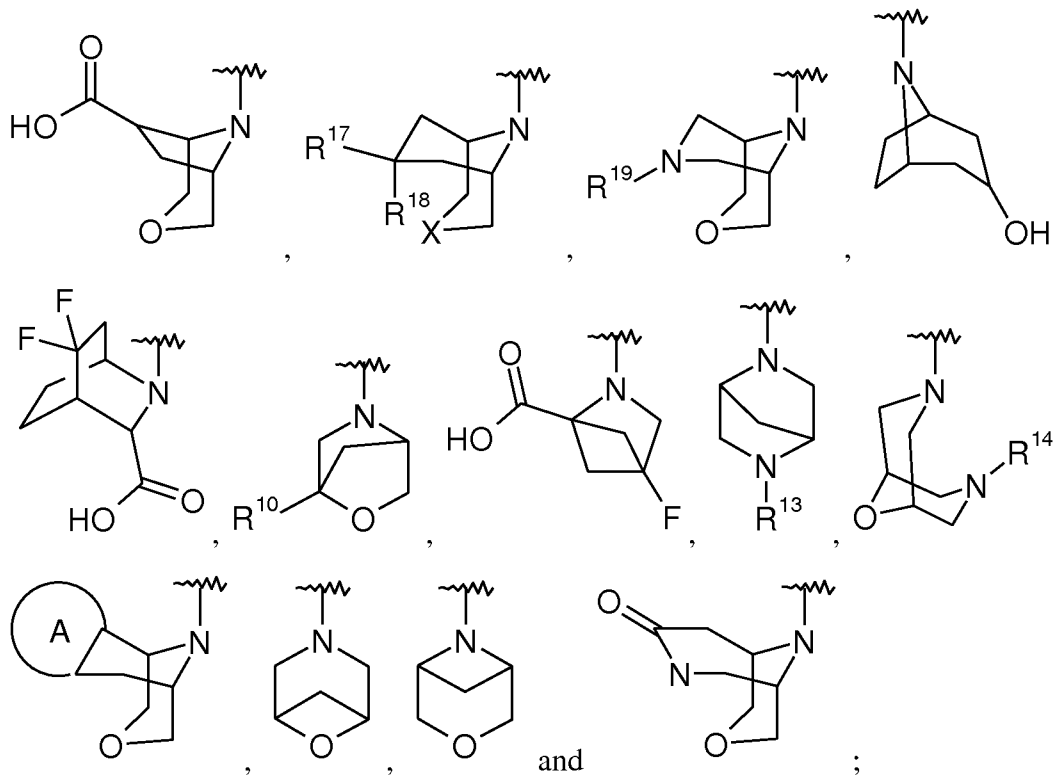
wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen;

R^3 is hydrogen or C_{1-6} alkyl;

R^4 is selected from



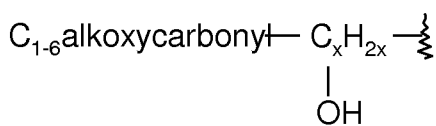
wherein R¹⁰ is hydroxy-C_yH_{2y}-;

5 R¹³ is C₁₋₆alkylcarbonyl;

R¹⁴ is C₁₋₆alkoxycarbonyl;

X is -O- or -S-; provided that

when X is -O-, R¹⁷ is hydrogen or hydroxy, R¹⁸ is C₁₋₆alkoxycarbonyl-C_yH_{2y-}, carboxy-C_yH_{2y-}, hydroxy-C_yH_{2y-}, C₁₋₆alkylcarbonyl-O-, C₁₋₆alkylcarbonylamino, C₁₋₆alkylsulfonylamino



10 or OH , or R^{17} and R^{18} , together with the carbon atom, to which



they are attached, form N ;

when X is -S-, R¹⁷ is hydrogen, R¹⁸ is carboxy-C_vH_{2v}-;

R¹⁹ is selected from aminocarbonyl; aminosulfonyl; C₁₋₆alkoxycarbonyl-C_yH_{2y}-; C₁₋₆alkyl, which is unsubstituted or substituted by fluoro; C₁₋₆alkylaminosulfonyl; C₁₋₆alkylcarbonyl; C₁₋

15 6alkylsulfonyl and hydroxy-C_xH_{2x}-carbonyl;

A is pyrazolyl or oxypyrazolyl, which is unsubstituted or substituted by C₁₋₆alkyl;

x is 1-6;

y is 0-6;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

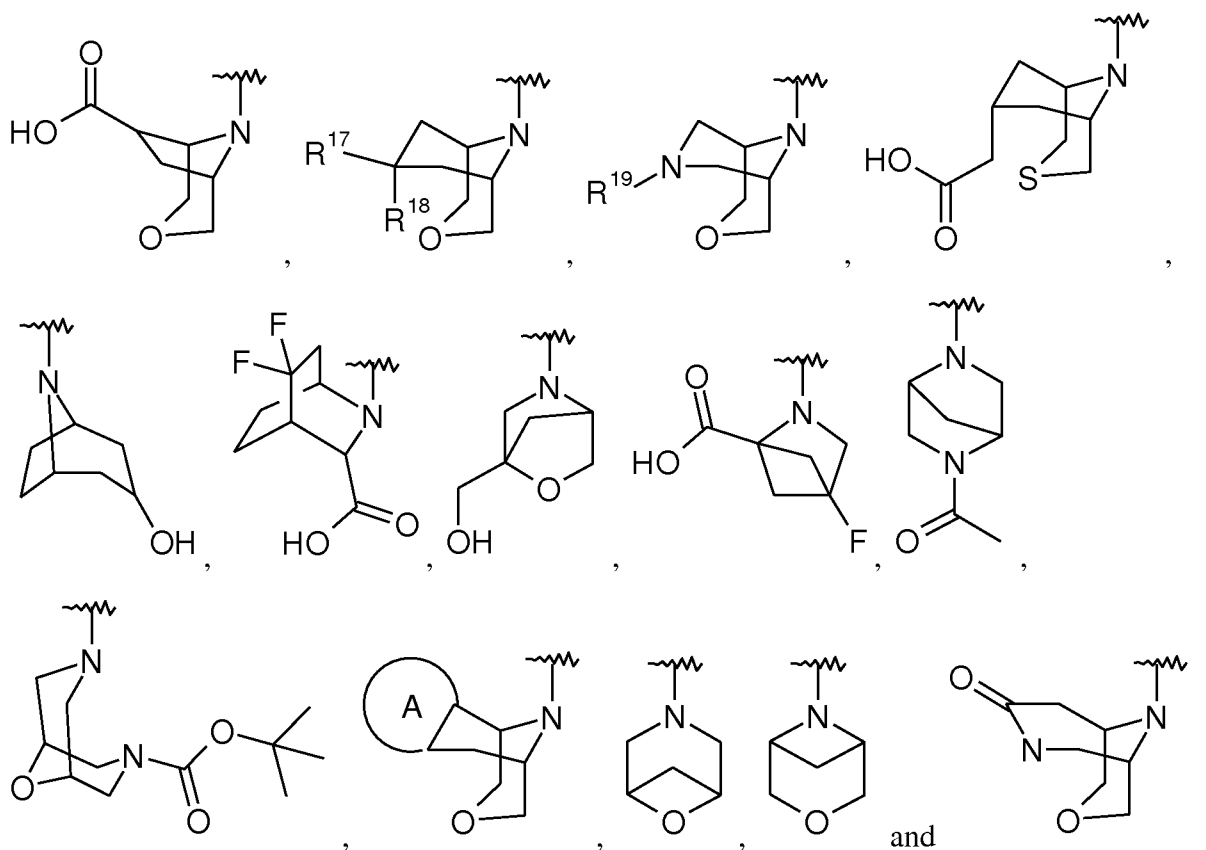
14. A compound according to claim 1 or 13, wherein

5 R^1 is methyl or ethyl;

R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro or bromo;

R^3 is hydrogen or methyl;

R^4 is selected from



wherein R^{17} is hydrogen or hydroxy;

R^{18} is methoxycarbonyl, methoxycarbonylmethyl, methoxycarbonylmethyl(hydroxy), carboxy, carboxymethyl, hydroxy, hydroxymethyl, methylcarbonyl-O-, methylcarbonylamino or
15 methylsulfonylamino;

or R^{17} and R^{18} , together with the carbon atom, to which they are attached, form  ;

R^{19} is aminocarbonyl, aminosulfonyl, methoxycarbonyl, ethoxycarbonylisopropyl, methyl, isopropyl, difluoroethyl, methylaminosulfonyl, methylcarbonyl, methylsulfonyl or hydroxymethylcarbonyl;

A is pyrazolyl or oxypyrazolyl, which is unsubstituted or substituted by methyl; or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

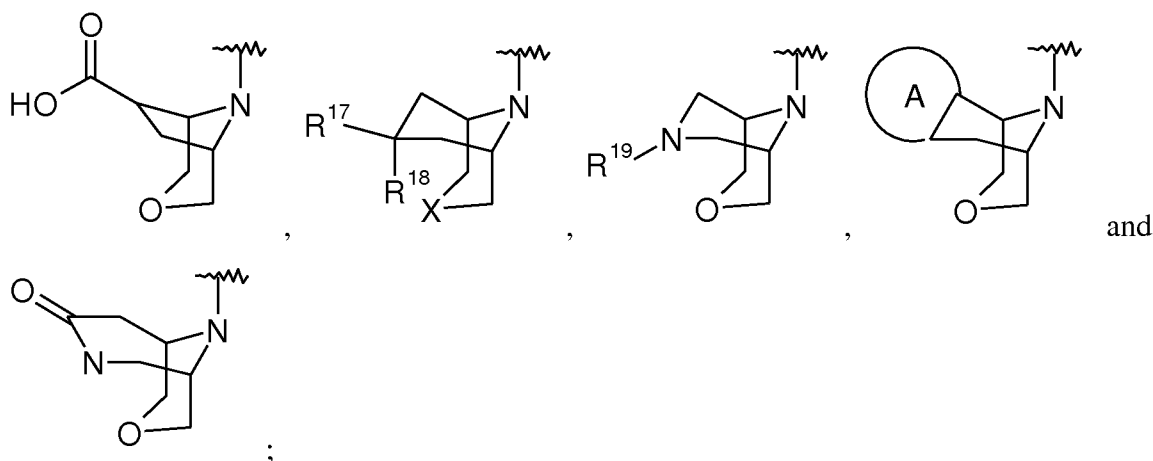
- 5 15. A compound according to claim 1 or 13 or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof, wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen;

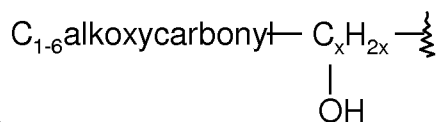
R^3 is hydrogen or C_{1-6} alkyl;

- 10 R^4 is selected from



X is -O- or -S-; provided that

- 15 when X is -O-, R^{17} is hydrogen or hydroxy, R^{18} is C_{1-6} alkoxycarbonyl- C_yH_{2y} -, carboxy- C_yH_{2y} -, hydroxy- C_yH_{2y} -, C_{1-6} alkylcarbonyl-O-, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino



or , or R^{17} and R^{18} , together with the carbon atom, to which

they are attached, form ;

when X is -S-, R^{17} is hydrogen, R^{18} is carboxy- C_yH_{2y} -;

- 20 R^{19} is selected from aminocarbonyl; aminosulfonyl; C_{1-6} alkoxycarbonyl- C_yH_{2y} -; C_{1-6} alkyl, which is unsubstituted or substituted by fluoro; C_{1-6} alkylaminosulfonyl; C_{1-6} alkylcarbonyl; C_{1-6} alkylsulfonyl and hydroxy- C_xH_{2x} -carbonyl;

A is pyrazolyl or oxypyrazolyl, which is unsubstituted or substituted by C_{1-6} alkyl;

x is 1-6;

-253-

y is 0-6.

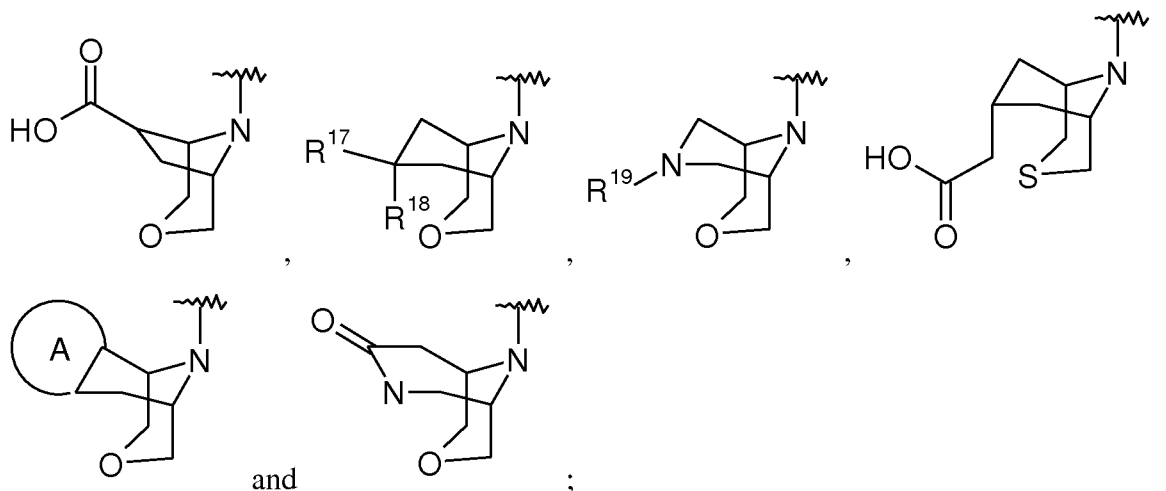
16. A compound according to any one of claims 1, 13, 14 or 15 or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof, wherein

R^1 is methyl or ethyl;

R^2 is phenyl, which is once or twice or three times substituted by fluoro, chloro or bromo;

R^3 is hydrogen or methyl;

R^4 is selected from



R^{17} is hydrogen or hydroxy;

R^{18} is methoxycarbonyl, methoxycarbonylmethyl, methoxycarbonylmethyl(hydroxy), carboxy, carboxymethyl, hydroxy, hydroxymethyl, methylcarbonyl-O-, methylcarbonylamino or methylsulfonylamino;

or R^{17} and R^{18} , together with the carbon atom, to which they are attached, form  ;
 R^{19} is aminocarbonyl, aminosulfonyl, methoxycarbonyl, ethoxycarbonylisopropyl, methyl, isopropyl, difluoroethyl, methylaminosulfonyl, methylcarbonyl, methylsulfonyl or hydroxymethylcarbonyl;

A is pyrazolyl or oxypyrazolyl, which is unsubstituted or substituted by methyl.

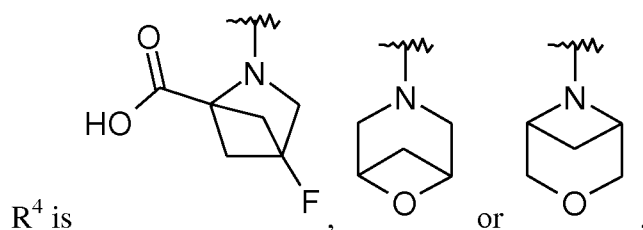
17. A compound according to claim 1 or 13 or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof, wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen;

R^3 is hydrogen;

-254-

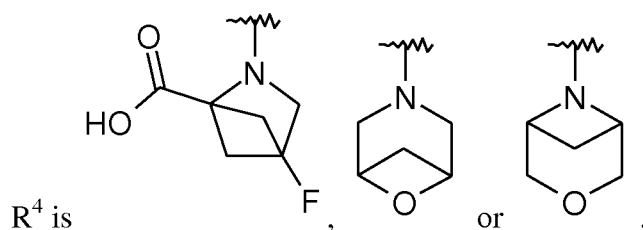


18. A compound according to any one of claims 1, 13, 14 or 17 or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof, wherein

5 R¹ is methyl;

R² is phenyl, which is once or twice or three times substituted by fluoro, chloro or bromo;

R³ is hydrogen;



10 19. A compound according to any one of claims 1 to 18, selected from

9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid;

9-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-(4-methyl-thiazol-2-yl)-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid;

15 9-[6-(3,4-Difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid;

9-[(R)-6-(2-Bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester;

20 9-[(R)-6-(2-Bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-9-aza-bicyclo[3.3.1]nonane-7-carboxylic acid;

8-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-8-aza-bicyclo[3.2.1]octane-6-carboxylic acid;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-hydroxy-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

25 (R)-6-(7-Acetoxy-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-hydroxy-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-hydroxy-7-hydroxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methanesulfonyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-isopropyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(2,2-difluoro-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Acetyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methylsulfamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

9-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester;

(R)-6-(7-Carbamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-sulfamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(1-ethoxycarbonyl-1-methyl-ethyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(2-hydroxy-acetyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

7-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester;

(S)-2-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-5,5-difluoro-2-aza-bicyclo[2.2.2]octane-3-carboxylic acid;

5 (R)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methoxycarbonylmethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

10 (R)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid ethyl ester;

6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(3,4-difluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

15 (R)-4-(2-Bromo-4-fluoro-phenyl)-6-(7-carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(S)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(3,4-difluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid ethyl ester;

20 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(hydroxy-methoxycarbonyl-methyl)-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

25 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(3-methyl-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(5-methyl-3-oxo-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodec-2(6)-en-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

30 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(4-oxo-8-oxa-3,10-diaza-bicyclo[4.3.1]dec-10-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Acetylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methanesulfonylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(2-methoxymethyl-azetidin-1-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(6-oxa-3-aza-bicyclo[3.1.1]hept-3-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(S)-3-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3,6-diaza-bicyclo[3.2.1]octane-7-carboxylic acid;

2-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-4-fluoro-2-aza-bicyclo[2.1.1]hexane-1-carboxylic acid;

(R)-6-(5-Acetyl-2,5-diaza-bicyclo[2.2.1]hept-2-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

6-(7-Carboxymethyl-3-thia-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Diazirine-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-((1R,3R,5S)-3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(9-oxa-3,4,11-triaza-tricyclo[5.3.1.0*2,6*]undeca-2(6),4-dien-11-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

2-[[[(1R,5S)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]oxy]acetic acid;

2-[[[(1R,5S)-9-[[[(4S)-4-(3,4-difluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]oxy]acetic acid;

Methyl (4R)-6-[(6-acetamido-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-hydroxy-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

2-[[[8-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]oxy]acetic acid;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-fluoro-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

8-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-6-carboxylic acid;

Methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-[[7-(2-hydroxyacetyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

5 Methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-[(7-carbamoyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

2-[(1R,5S)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

10 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(1R,5S)-7-endo-(sulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-6-[(1S,5R)-7-endo-ureido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-1,4-dihydropyrimidine-5-carboxylate;

2-[(1S,5R)-9-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

15 Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(1R,5S)-7-exo-(methanesulfonamido)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

20 Methyl (4R)-6-[(1S,5R)-7-exo-acetamido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-6-[(1S,5R)-7-exo-ureido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(1R,5S)-7-exo-(sulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

25 2-[(1R,5S,6S)-8-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]acetic acid;

Endo-2-[(1S,5R)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

30 Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromo-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

5 Ethyl (4R)-6-[[[(1S,5R)-7-endo-acetamido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-bromo-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Ethyl (4R)-6-[[[(1S,5R)-7-exo-acetamido-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-4-(2-bromo-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

10 Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromo-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

15 Exo-2-[(1S,5R)-9-[[[(4R)-4-(2,3-difluorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

20 Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

25 3-[(1S,5R)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl]-2,2-dimethyl-3-oxo-propanoic acid;

Exo-2-[(1S,5R)-9-[[[(4R)-4-(2-bromo-3,4-difluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

(1S,5R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

30 (1R,5S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

(1S,5R)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

(1R,5S)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

5 2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

10 2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chlorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

15 2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chlorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[[(4R)-4-(2-bromophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

20 2-[(1S,3R,5R)-8-[[[(4R)-4-(2-bromophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R, 3S,5S)-8-[[[(4R)-4-(2-bromo-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S, 3R,5R)-8-[[[(4R)-4-(2-bromo-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

25 2-[(1R,3S,5S)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

30 2-[(1R,3S,5S)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,5S,6R,7R)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(1R,5R,6S,7S)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

5 2-[(1S,5S,6R,7R)-9-[[[(4R)-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(1R,5R,6S,7S)-9-[[[(4R)-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-fluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

10 (4R)-4-(2-Chloro-4-fluoro-phenyl)-6-(4,10-dioxa-5,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2,5-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(4R)-4-(2-Chloro-4-fluoro-phenyl)-6-(5,10-dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

15 (4R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-fluoro-5,10-dioxa-4,12-diaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7,7-difluoro-10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

20 Methyl (4R)-4-(2-chloro-4-fluorophenyl)-6-[(6,6-difluoro-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-(1,3-thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate;

2-[(1R,3R,5S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3S,5R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

25 2-[(1R,3R,5S)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3S,5R)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

30 2-[(1R,3R,5S)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid or 2-[(1S,3S,5R)-8-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[[(4S)-4-(3,4-difluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[[(4S)-4-(3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

5 2-[(3R)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3S)-8-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

10 2-[(3R)-8-[[[(4R)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3S)-8-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

15 2-[(3R)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3S)-8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

Methyl (4R)-6-[(3-acetyl-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

25 2-[(7S)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7R)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7R)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

30 2-[(7S)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7R)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7S)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7R)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

5 2-[(7S)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(1R,5R,7S)-9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid or 2-[(1S,5S,7R)-9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-10 2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(1R,5R,7S)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid or 2-[(1S,5S,7R)-9-[[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-15 2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Endo-2-[9-[[[(4R)-4-(2-bromophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Endo-2-[9-[[[(4R)-4-(2-chloro-3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Endo-2-[9-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

25 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-1-hydroxy-2-oxo-ethyl)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-6,7-dihydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

30 7-amino-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid;

7-amino-9-[[[(4R)-4-(2,3-difluorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid;

7-amino-9-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-(8-oxa-3-azabicyclo[3.2.1]octan-3-ylmethyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

5 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(5,5-difluoro-3-azabicyclo[2.2.1]heptan-3-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

10 Methyl (4R)-6-[[4-(acetamidomethyl)-5-oxa-2-azabicyclo[2.2.1]heptan-2-yl]methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-7-(methanesulfonamido)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

15 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-7-[(2,2,2-trifluoroacetyl)amino]-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

(1S,4R)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylic acid;

(1R,4S)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylic acid;

20 8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

(5S)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-5-carboxylic acid; and

25 (5R)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-5-carboxylic acid.

20. A compound according to any one of claims 1 to 19, selected from

30 9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonane-7-carboxylic acid;

8-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-3,6-dihydropyrimidin-4-ylmethyl]-3-oxa-8-aza-bicyclo[3.2.1]octane-6-carboxylic acid;

(R)-6-(7-Carbamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-sulfamoyl-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

5 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-[7-(2-hydroxy-acetyl)-3-oxa-7,9-diaza-bicyclo[3.3.1]non-9-ylmethyl]-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

10 (R)-6-(7-Carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid ethyl ester;

(R)-4-(2-Bromo-4-fluoro-phenyl)-6-(7-carboxymethyl-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

15 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(10-oxa-4,5,12-triaza-tricyclo[6.3.1.0*2,6*]dodeca-2(6),3-dien-12-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(4-oxo-8-oxa-3,10-diaza-bicyclo[4.3.1]dec-10-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-6-(7-Acetylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

20 (R)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methanesulfonylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

2-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-4-fluoro-2-aza-bicyclo[2.1.1]hexane-1-carboxylic acid;

25 6-(7-Carboxymethyl-3-thia-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(9-oxa-3,4,11-triaza-tricyclo[5.3.1.0*2,6*]undeca-2(6),4-dien-11-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

30 2-[[[(1R,5S)-9-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]oxy]acetic acid;

2-[[[8-[[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]oxy]acetic acid;

8-[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-6-carboxylic acid;

Methyl (4R)-4-(2-bromo-4-fluoro-phenyl)-6-[(7-carbamoyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

5 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(1R,5S)-7-endo-(sulfamoylamino)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(1R,5S)-7-exo-(methanesulfonamido)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

10 2-[(1R,5S,6S)-8-[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]acetic acid;

Exo-2-[(1S,5R)-9-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

Exo-2-[(1S,5R)-9-[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

15 (1S,5R)-8-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

(1R,5S)-8-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid;

20 2-[(1R,3S,5S)-8-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

25 2-[(1S,3R,5R)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

30 2-[(1S,3R,5R)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3R,5S)-8-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3S,5R)-8-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1R,3S,5S)-8-[[(4S)-4-(3,4-difluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

5 2-[(1S,3R,5R)-8-[[(4S)-4-(3,4-difluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3R)-8-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

10 2-[(3S)-8-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3R)-8-[[(4R)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

15 2-[(3S)-8-[[(4S)-4-(3,4-difluoro-2-methyl-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

20 2-[(3R)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(3S)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

25 2-[(7R)-9-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

2-[(7S)-9-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid;

30 Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[[7-(2-ethoxy-2-oxo-ethyl)-7-(methanesulfonamido)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl]methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

(1S,4R)-7-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylic acid;

-268-

(1R,4S)-7-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-2,2-difluoro-7-azabicyclo[2.2.1]heptane-4-carboxylic acid;

8-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

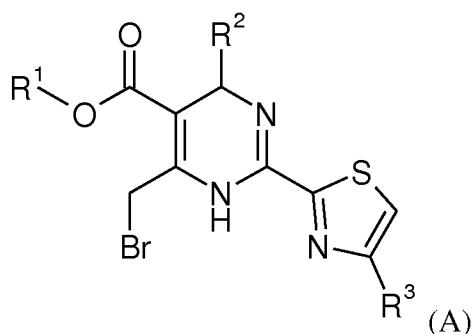
5 2-[(7R)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid; and

2-[(7S)-9-[[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]acetic acid.

10

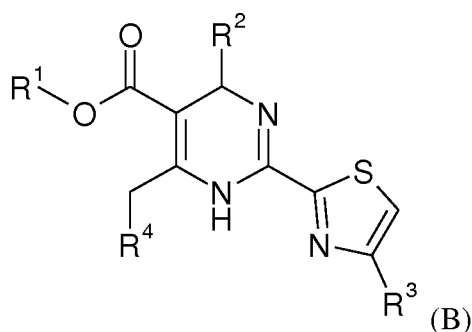
21. A process for the preparation of a compound according to any one of claims 1 to 20 comprising the reaction of

(a) a compound of formula (A)



with bridged amine in the presence of a base;

(b) a compound of formula (B)



under chiral separation condition;

wherein R¹ to R⁴ are defined as in any one of claims 1 to 18.

22. A compound according to any one of claims 1 to 20 for use as therapeutically active substance.

23. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 20 and a therapeutically inert carrier.

5 24. The use of a compound according to any one of claims 1 to 20 for the treatment or prophylaxis of hepatitis B virus infection.

25. The use of a compound according to any one of claims 1 to 20 for the preparation of a medicament for the treatment or prophylaxis of hepatitis B virus infection.

10

26. A compound according to any one of claims 1 to 20 for the treatment or prophylaxis of hepatitis B virus infection.

15

27. A compound according to any one of claims 1 to 20, when manufactured according to a process of claim 21.

28. A method for the treatment or prophylaxis of hepatitis B virus infection, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 20.

20

29. The invention as hereinbefore described.