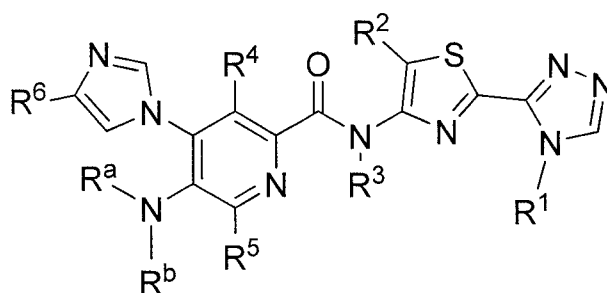


thereof and methods for treating autoimmune disorders, inflammatory diseases, cardiovascular diseases and neurodegenerative diseases.

SUMMARY

The present invention provides novel compounds that function as ASK1 inhibitors, compositions and methods of using said novel compounds. In a first aspect, the invention relates to compounds of Formula (I):



(I)

wherein:

R¹ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl, wherein the alkyl or cycloalkyl is optionally substituted with one to three halogen atoms;

R² is hydrogen or C₁-C₆ alkyl wherein the alkyl is optionally substituted with halo.

R³ is hydrogen or C₁-C₃ alkyl;

R⁴ is hydrogen or C₁-C₃ alkyl;

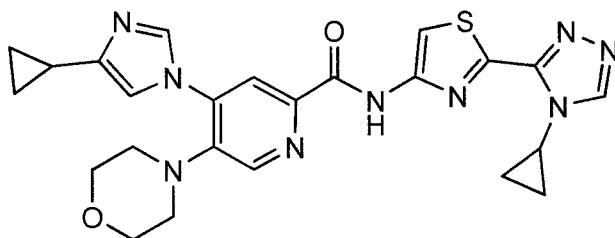
R⁵ is hydrogen, C₁-C₃ alkyl, OR^a or -NHR^a;

R⁶ is hydrogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₆ cycloalkyl wherein the cycloalkyl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ haloalkyl, or 1 or 2 halogen atoms;

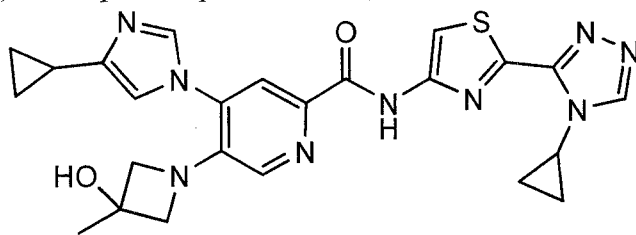
R^a and R^b are independently hydrogen, C₁-C₃ alkyl or R^a and R^b combine with the nitrogen atom to which they are attached to form a four to six member heterocyclic ring optionally containing an oxygen or a nitrogen atom in the ring;

or a pharmaceutically acceptable salt or stereoisomer thereof.

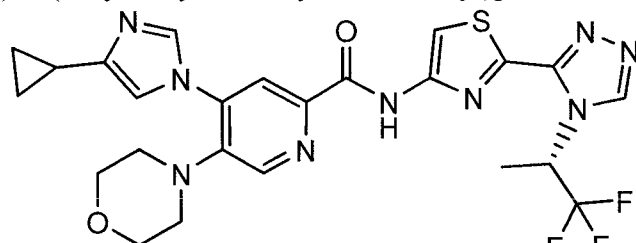
In a second aspect, the invention relates to a compound selected from the group consisting of:



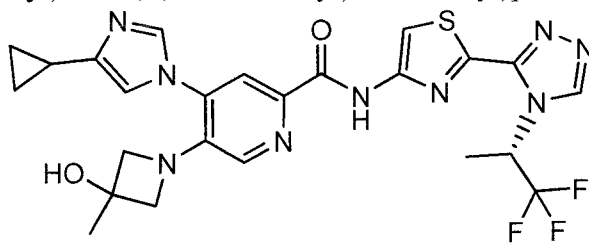
, namely
4-(4-cyclopropyl-1H-imidazol-1-yl)-N-(2-(4-cyclopropyl-4H-1,2,4-triazol-3-yl)thiazol-4-yl)-5-morpholinopicolinamide;



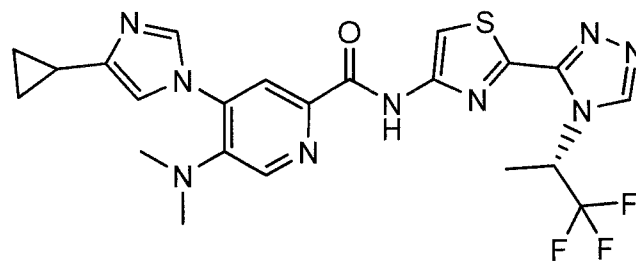
, namely
4-(4-cyclopropyl-1H-imidazol-1-yl)-N-(2-(4-cyclopropyl-4H-1,2,4-triazol-3-yl)thiazol-4-yl)-5-(3-hydroxy-3-methylazetidin-1-yl)picolinamide;



, namely
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-morpholino-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;

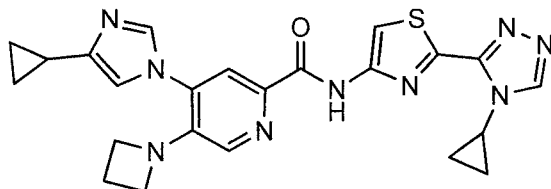


, namely
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(3-hydroxy-3-methylazetidin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;
and

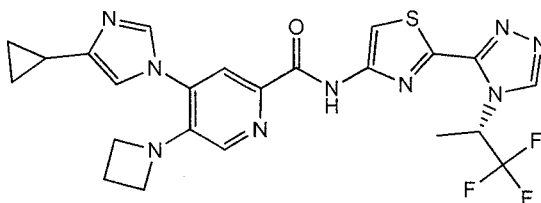


, namely
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(dimethylamino)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide; or a
pharmaceutically acceptable salt or enantiomer thereof.

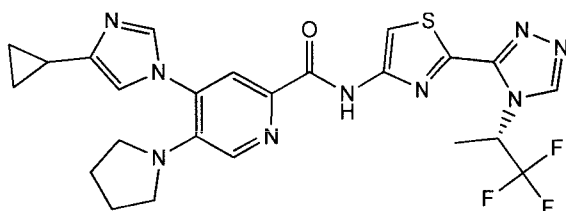
In a third aspect, the invention relates to a compound selected from the group consisting of:



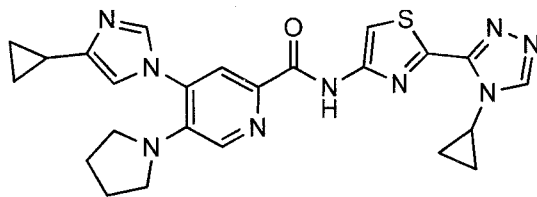
5-(azetidin-1-yl)-4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]pyridine-2-carboxamide;



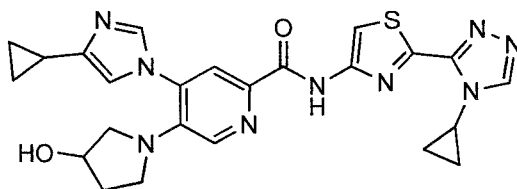
(S)-5-(azetidin-1-yl)-4-(4-cyclopropyl-1H-imidazol-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;



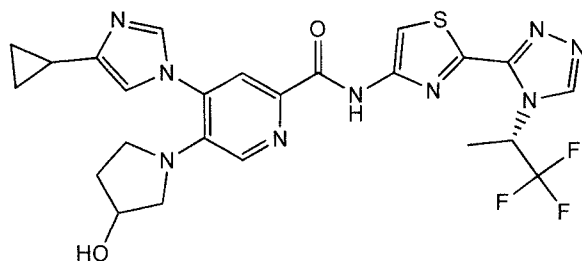
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(pyrrolidin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;



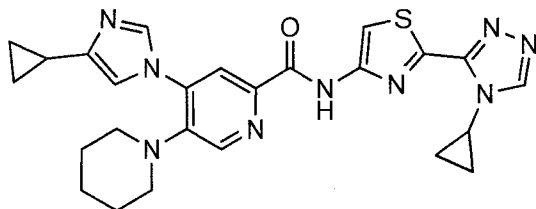
4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]-5-pyrrolidin-1-ylpyridine-2-carboxamide;



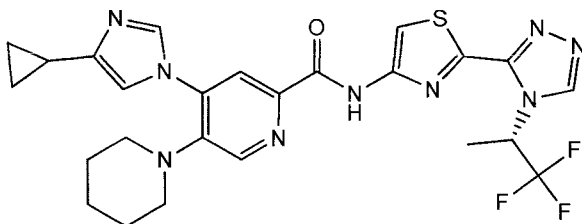
4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]-5-(3-hydroxypyrrolidin-1-yl)pyridine-2-carboxamide;



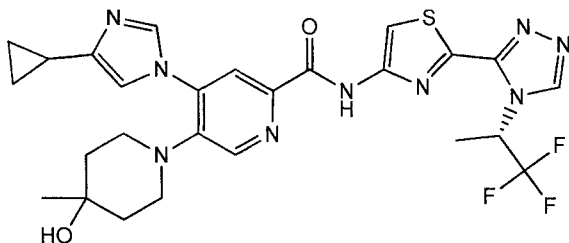
4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(3-hydroxypyrrolidin-1-yl)-N-(2-(4-((S)-1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;



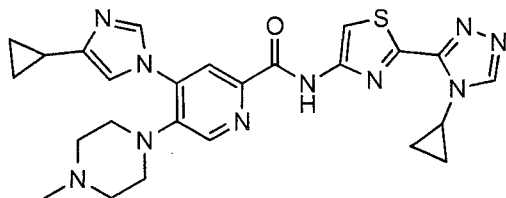
4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]-5-piperidin-1-ylpyridine-2-carboxamide;



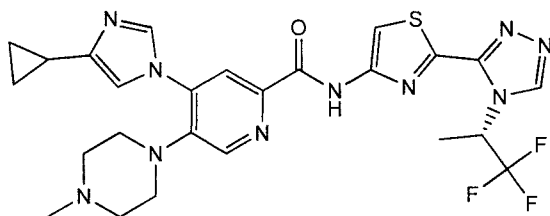
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(piperidin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;



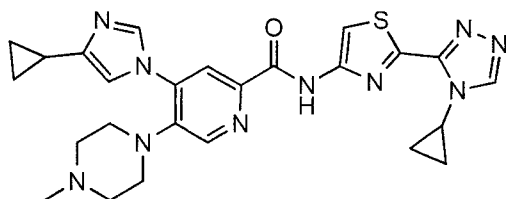
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(4-hydroxy-4-methylpiperidin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;



4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]-5-(4-hydroxy-4-methylpiperidin-1-yl)pyridine-2-carboxamide;



(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide; and



4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]-5-(4-methylpiperazin-1-yl)pyridine-2-carboxamide;
or a pharmaceutically acceptable salt or stereoisomer thereof.

The disclosure also relates to a method of using the compounds of Formula (I) in the treatment of a disease or condition in a patient, preferably a human patient, which is amenable to treatment by an ASK1 inhibitor. Such diseases include autoimmune disorders, inflammatory diseases, cardiovascular diseases (including

diabetes, diabetic nephropathy, and other complications of diabetes), cardio-renal diseases, including kidney disease, fibrotic diseases, respiratory diseases (including COPD, idiopathic pulmonary fibrosis (IPF), and acute lung injury), acute and chronic liver diseases, and neurodegenerative diseases.

In a fourth aspect, the invention relates to pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) and at least one pharmaceutically acceptable excipient.

The disclosure also provides a compound of formula (I) useful for treating chronic kidney disease.

The disclosure further provides a compound of formula (I) useful for treating kidney fibrosis.

In another aspect, the invention provides a compound of formula (I) for use in therapy.

The disclosure further relates to the use of a compound of formula (I) for the manufacture of a medicament for treating autoimmune disorders, inflammatory diseases, cardiovascular diseases (including diabetes, diabetic nephropathy, and other complications of diabetes), cardio-renal diseases, including kidney disease, fibrotic diseases, respiratory diseases (including COPD, idiopathic pulmonary fibrosis (IPF), and acute lung injury), acute and chronic liver diseases, and neurodegenerative diseases.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Parameters

As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

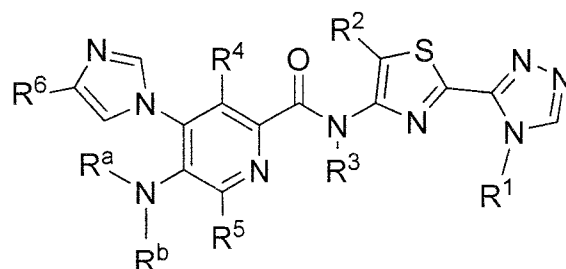
The term “alkyl” refers to a monoradical branched or unbranched saturated hydrocarbon chain having the indicated number of carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl and the like.

The term “substituted alkyl” refers to:

- 1) an alkyl group as defined above, having 1, 2, or 3 substituents selected from the indicated groups.

CLAIMS:

1. A compound of Formula (I):



(I)

wherein:

- R¹ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl, wherein the alkyl or cycloalkyl is optionally substituted with one to three halogen atoms;
- R² is hydrogen or C₁-C₆ alkyl wherein the alkyl is optionally substituted with halo;
- R³ is hydrogen or C₁-C₃ alkyl;
- R⁴ is hydrogen or C₁-C₃ alkyl;
- R⁵ is hydrogen, C₁-C₃ alkyl, OR^a or -NHR^a;
- R⁶ is hydrogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₆ cycloalkyl wherein the cycloalkyl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ haloalkyl, or 1 or 2 halogen atoms;
- R^a and R^b are independently hydrogen, C₁-C₃ alkyl or R^a and R^b combine with the nitrogen atom to which they are attached to form a four to six member heterocyclic ring optionally containing an oxygen or a nitrogen atom in the ring;
- or a pharmaceutically acceptable salt or stereoisomer thereof.

2. The compound according to Claim 1 wherein:

- R¹ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl, wherein the alkyl or cycloalkyl is optionally substituted with one to three halogen atoms;
- R² is hydrogen;
- R³ is hydrogen;
- R⁴ and R⁵ are both hydrogen;
- R⁶ is C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;
- R^a and R^b are independently hydrogen or C₁-C₃ alkyl; or R^a and R^b combine with the nitrogen atom to which they are attached to form a four to six member heterocyclic group optionally containing an oxygen atom in the ring; wherein the heterocyclic group is further optionally substituted with one or two groups independently selected from C₁-C₃ alkyl and

hydroxyl;

or a pharmaceutically acceptable salt or stereoisomer thereof.

3. The compound according to Claim 1 wherein:

R^1 is C_1 - C_3 alkyl or cyclopropyl, wherein the alkyl group is substituted with three fluoro atoms;

R^2 is hydrogen;

R^3 is hydrogen;

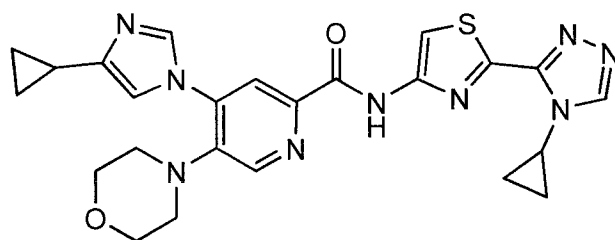
R^4 and R^5 are both hydrogen;

R^6 is cyclopropyl;

R^a and R^b are both C_1 - C_3 alkyl or R^a and R^b combined with the nitrogen atom to which they are attached to form a four to six member heterocyclic group optionally containing an oxygen atom in the ring; wherein the heterocyclic group is further optionally substituted with one or two groups selected from C_1 - C_3 alkyl and hydroxyl;

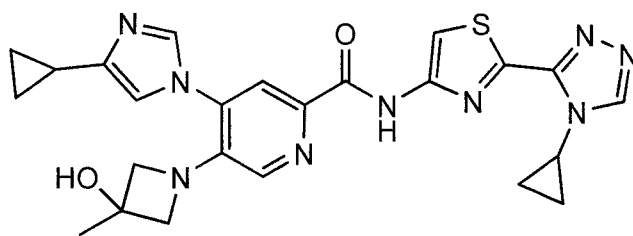
or a pharmaceutically acceptable salt or stereoisomer thereof.

4. The compound selected from the group consisting of:



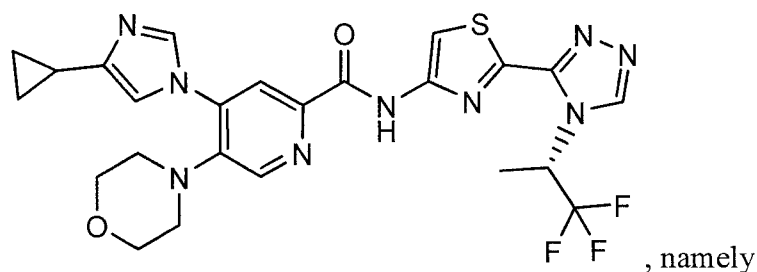
, namely

4-(4-cyclopropyl-1H-imidazol-1-yl)-N-(2-(4-cyclopropyl-4H-1,2,4-triazol-3-yl)thiazol-4-yl)-5-morpholinopicolinamide;

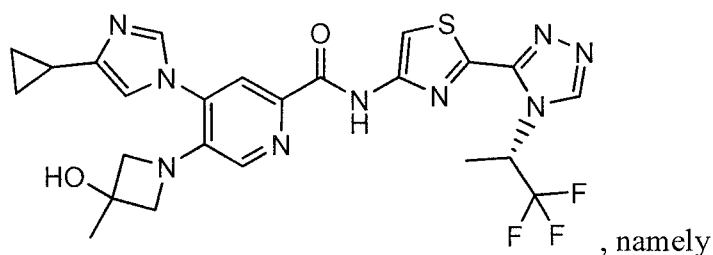


, namely

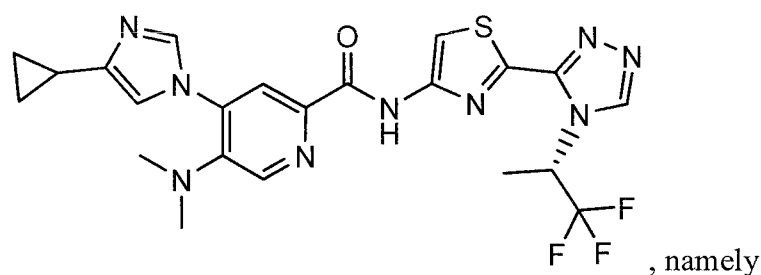
4-(4-cyclopropyl-1H-imidazol-1-yl)-N-(2-(4-cyclopropyl-4H-1,2,4-triazol-3-yl)thiazol-4-yl)-5-(3-hydroxy-3-methylazetidin-1-yl)picolinamide;



(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-morpholino-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;

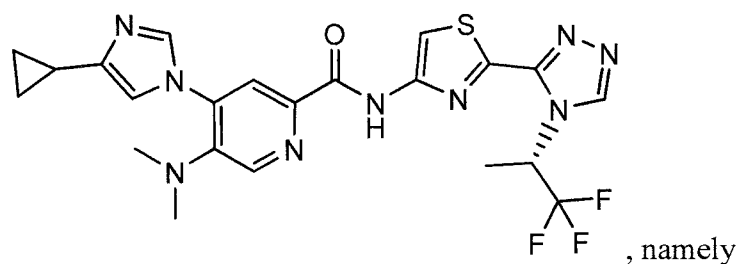


(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(3-hydroxy-3-methylazetidin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide; and



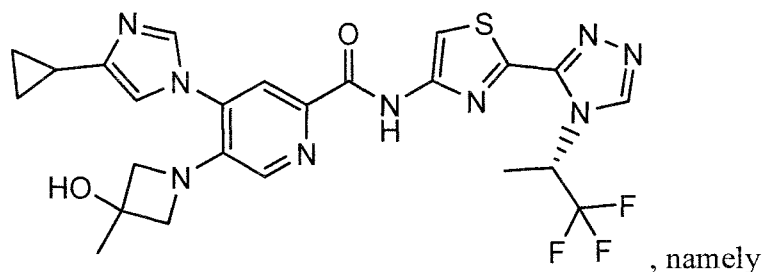
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(dimethylamino)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide; or a pharmaceutically acceptable salt or enantiomer thereof.

5. The compound of Claim 4, wherein the compound is



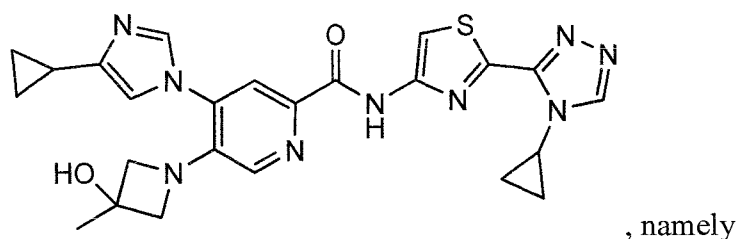
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(dimethylamino)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide or a pharmaceutically acceptable salt or enantiomer thereof.

6. The compound of Claim 4, wherein the compound is



(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(3-hydroxy-3-methylazetidin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide or a pharmaceutically acceptable salt or enantiomer thereof.

7. The compound of Claim 4, wherein the compound is



4-(4-cyclopropyl-1H-imidazol-1-yl)-N-(2-(4-cyclopropyl-4H-1,2,4-triazol-3-yl)thiazol-4-yl)-5-(3-hydroxy-3-methylazetidin-1-yl)picolinamide or a pharmaceutically acceptable salt or enantiomer thereof.

8. The compound according to Claim 1, wherein

R^1 is C_1 - C_3 alkyl or cyclopropyl, wherein alkyl or cyclopropyl is optionally substituted with one to three fluoro atoms;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 and R^5 are both hydrogen;

R^6 is C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, or cyclopropyl, wherein cyclopropyl is substituted with one to two fluoro atoms;

R^a and R^b are combined with the nitrogen atom to which they are attached to form a

heterocyclic group selected from the group consisting of azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl; wherein the heterocyclic group is further optionally substituted with one or two groups selected from C₁-C₃ alkyl and hydroxyl;

or a pharmaceutically acceptable salt or stereoisomer thereof.

9. The compound according to Claim 1, wherein

R¹ is methyl, ethyl, propyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, fluoropropyl, difluoropropyl, trifluoropropyl, fluorocyclopropyl, difluorocyclopropyl, or cyclopropyl;

R² is hydrogen;

R³ is hydrogen;

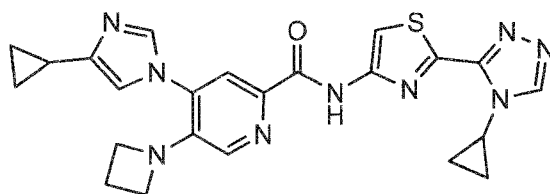
R⁴ and R⁵ are both hydrogen;

R⁶ is methyl, ethyl, propyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, fluoropropyl, difluoropropyl, trifluoropropyl, fluorocyclopropyl, difluorocyclopropyl, or cyclopropyl;

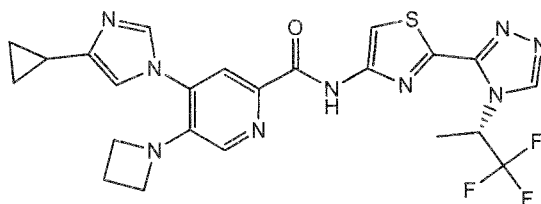
R^a and R^b are combined with the nitrogen atom to which they are attached to form a heterocyclic group selected from the group consisting of azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl; wherein the heterocyclic group is further optionally substituted with one or two groups selected from methyl, ethyl, propyl, and hydroxyl;

or a pharmaceutically acceptable salt or stereoisomer thereof.

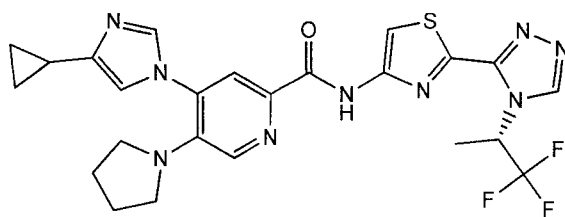
10. A compound selected from the group consisting of:



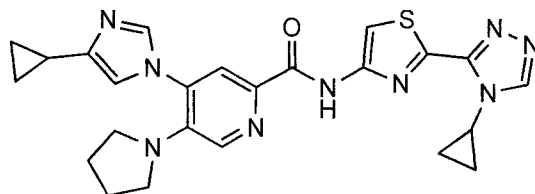
5-(azetidin-1-yl)-4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]pyridine-2-carboxamide;



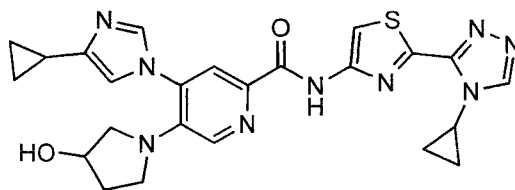
(S)-5-(azetidin-1-yl)-4-(4-cyclopropyl-1H-imidazol-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;



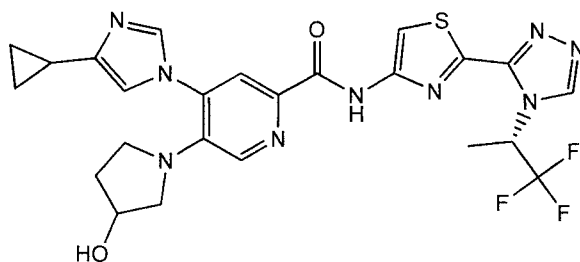
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(pyrrolidin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;



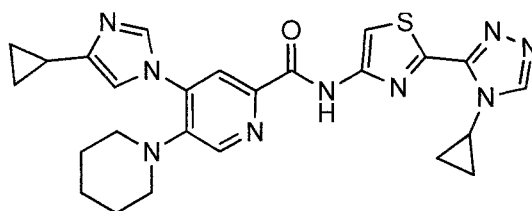
4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]-5-pyrrolidin-1-ylpyridine-2-carboxamide;



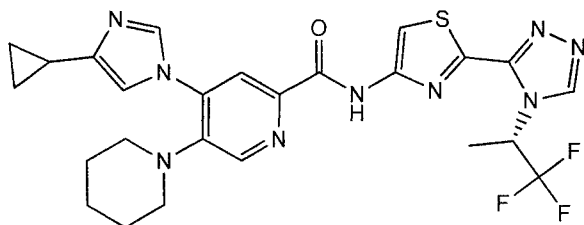
4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]-5-(3-hydroxypyrrolidin-1-yl)pyridine-2-carboxamide;



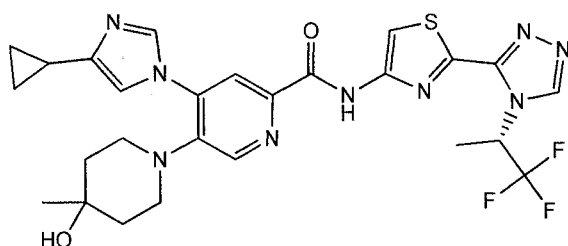
4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(3-hydroxypyrrolidin-1-yl)-N-(2-(4-((S)-1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;



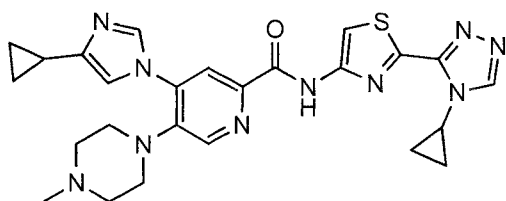
4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]-5-piperidin-1-ylpyridine-2-carboxamide;



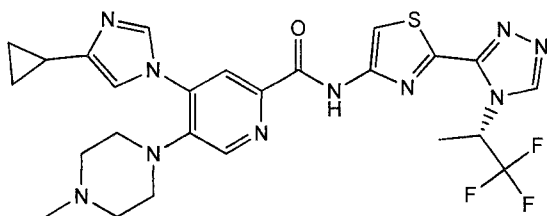
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(piperidin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;



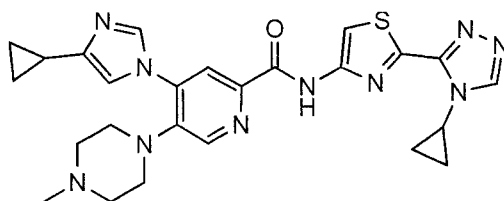
(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(4-hydroxy-4-methylpiperidin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide;



4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]-5-(4-hydroxy-4-methylpiperidin-1-yl)pyridine-2-carboxamide;



(S)-4-(4-cyclopropyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)-N-(2-(4-(1,1,1-trifluoropropan-2-yl)-4H-1,2,4-triazol-3-yl)thiazol-4-yl)picolinamide; and



4-(4-cyclopropylimidazol-1-yl)-N-[2-(4-cyclopropyl-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]-5-(4-methylpiperazin-1-yl)pyridine-2-carboxamide;

or a pharmaceutically acceptable salt or stereoisomer thereof.

11. A pharmaceutical composition comprising a compound according to Claims 1-10 and at least one pharmaceutically acceptable excipient.

12. A compound according to Claims 1-10 for use in therapy.