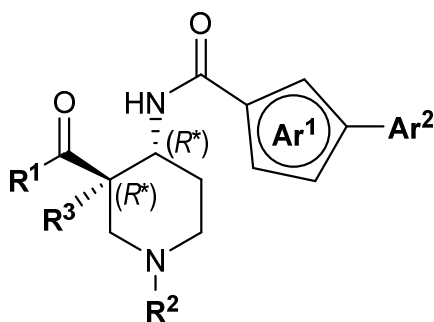


Claims

1. A compound of formula (I)



Formula (I)

5 wherein

the two substituents of the piperidine ring: R^1 -CO- and -NH-CO- Ar^1 - Ar^2 , are in relative *trans*-configuration;

Ar^1 represents an unsubstituted 5-membered heteroarylene group containing one sulfur ring atom and one or two nitrogen ring atoms, wherein the -NH-CO- group and Ar^2 are attached in *meta* arrangement to ring atoms of Ar^1 ;

Ar^2 represents phenyl, or 6-membered heteroaryl; wherein said phenyl or 6-membered heteroaryl independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from fluoro, chloro, methyl, cyano, methoxy, or (C_1) fluoroalkyl;

R^1 represents $R^{N1}R^{N2}N$ -, wherein

• R^{N1} represents

- hydrogen;
- (C_{1-6}) alkyl;
- (C_{1-6}) alkyl which is mono-substituted with

- hydroxy;
- (C_{1-3}) alkoxy;
- 2-hydroxy-ethoxy;
- -CO-NH₂;
- -SO₂-(C_{1-3})alkyl;
- cyano;
- (C_{1-3}) fluoroalkoxy;
- -NR^{N3}R^{N4}, wherein R^{N3} and R^{N4} independently represent hydrogen or (C_{1-4}) alkyl;

- (C_{2-6}) alkynyl;

- (C₂₋₅)fluoroalkyl;
- (C₁₋₄)alkoxy;
- 2-(2-oxo-pyrrolidin-1-yl)-ethyl;
- a group -L¹-Cy¹; wherein

5 ▪ L¹ represents a direct bond, -(C₁₋₃)alkylene-, or -(C₃₋₅)cycloalkylene-; and

 ▪ Cy¹ represents (C₃₋₆)cycloalkyl, wherein said (C₃₋₆)cycloalkyl optionally contains one ring oxygen atom; wherein said (C₃₋₆)cycloalkyl independently is unsubstituted; or mono-substituted with fluoro, methyl, or hydroxy, -CO-(C₁₋₄)alkoxy, or cyano; or di-substituted with fluoro, or tri-

10 substituted with methyl and two fluoro;

- a group -L²-Ar³, wherein

 ▪ L² represents a direct bond, -(C₁₋₄)alkylene-; *- (C₃₋₅)cycloalkylene-(C₀₋₂)alkylene- wherein said (C₃₋₅)cycloalkylene optionally contains one ring oxygen atom, wherein the asterisk indicates the bond to which Ar³ is attached; *(C₁₋₂)alkylene-(C₃₋₅)cycloalkylene- wherein said (C₃₋₅)cycloalkylene optionally contains one ring oxygen atom, wherein the asterisk indicates the bond to which Ar³ is attached; or -(C₁₋₃)alkylene- which is mono-substituted with hydroxy, trifluoromethyl, or -CO-(C₁₋₄)alkoxy; and

15 ▪ Ar³ represents phenyl, or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, hydroxy, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; wherein, in case Ar³ represents 6-membered

20 heteroaryl which is pyridyl or pyrimidinyl, such pyridyl or pyrimidinyl may additionally be present in form of the respective N-oxide;

25 and R^{N2} independently represents hydrogen, (C₁₋₄)alkyl, or (C₂₋₃)fluoroalkyl;

- or R^{N1} and R^{N2} together with the nitrogen atom to which they are attached to form a 4- to 6-membered ring selected from

30 ➤ azetidiny, pyrrolidinyl or piperidinyl; each independently

- unsubstituted;
 - or mono-substituted with fluoro, methyl, or hydroxy;
 - or di-substituted with fluoro;
 - or mono-substituted with Ar⁴, wherein Ar⁴ represents phenyl, or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, or mono-, or di-substituted;
- 35

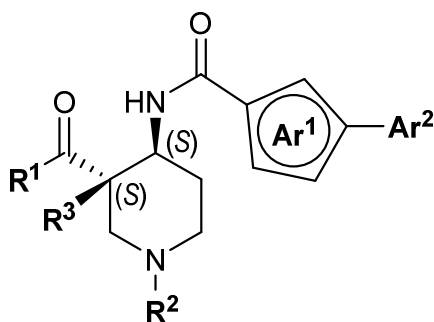
wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; or

➤ morpholinyl;

R² represents

- 5 • hydrogen;
 - (C₁₋₆)alkyl;
 - (C₂₋₆)alkyl which is mono-substituted with (C₁₋₃)alkoxy, or hydroxy;
 - (C₃₋₅)alkenyl;
 - cyano-methyl;
 - 10 • (C₂₋₃)fluoroalkyl;
 - (C₃₋₈)cycloalkyl-(C₀₋₃)alkyl; wherein the (C₃₋₈)cycloalkyl is unsubstituted, or mono- or di-substituted wherein the substituents are independently selected from (C₁₋₃)alkyl, fluoro, hydroxy, hydroxy-(C₁₋₃)alkyl, (C₁₋₃)alkoxy, or (C₁₋₃)fluoroalkyl;
 - thietan-3-yl;
 - 15 • (C₃₋₈)cycloalkenyl-(C₁₋₃)alkyl; or
 - **Ar⁵-CH₂-** wherein **Ar⁵** represents phenyl, or 5- or 6-membered heteroaryl, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, or mono- or di-substituted wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; and
 - 20 **R³** represents hydrogen, or methyl;
- or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) as defined for claim 1 which are also compounds of Formula (I_S), wherein the two substituents of the piperidine ring: R¹-CO- and -NH-CO-Ar¹-Ar², are in relative *trans*-configuration, wherein the absolute configuration of the two chiral carbon atoms in position 3 and 4 of the piperidine ring is (3S,4S):



Formula (I_S);

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2; wherein **R³** represents hydrogen; or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3; wherein **Ar¹** represents [1,3,4]thiadiazol-2,5-diyl or isothiazol-3,5-diyl;

5 or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4; wherein **Ar²** represents phenyl which is mono-, di- or tri-substituted; wherein one or two of said substituents is / are independently selected from fluoro, chloro, and methyl, and the remaining, if present, is / are fluoro; or a pharmaceutically acceptable salt thereof.

10 6. A compound according to any one of claims 1 to 5; wherein **R¹** represents **R^{N1}R^{N2}N-**, wherein

• **R^{N1}** represents

➤ (C₁₋₆)alkyl;

➤ (C₁₋₆)alkyl which is mono-substituted with

15

▪ hydroxy;

▪ (C₁₋₃)alkoxy;

▪ 2-hydroxy-ethoxy;

▪ -CO-NH₂;

▪ -SO₂-(C₁₋₃)alkyl;

20

▪ cyano;

▪ (C₁₋₃)fluoroalkoxy;

▪ -NR^{N3}R^{N4}, wherein **R^{N3}** and **R^{N4}** independently represent hydrogen or (C₁₋₄)alkyl;

➤ (C₂₋₆)alkynyl;

25

➤ (C₂₋₅)fluoroalkyl;

➤ 2-(2-oxo-pyrrolidin-1-yl)-ethyl;

➤ a group -**L¹**-**Cy¹**; wherein

▪ **L¹** represents a direct bond, -(C₁₋₃)alkylene-, or -(C₃₋₅)cycloalkylene-; and

▪ **Cy¹** represents (C₃₋₆)cycloalkyl, wherein said (C₃₋₆)cycloalkyl optionally contains one ring oxygen atom; wherein said (C₃₋₆)cycloalkyl independently is unsubstituted: or mono-substituted with fluoro, methyl, hydroxy, CO-(C₁₋₄)alkoxy, or cyano; or di-substituted with fluoro, or tri-substituted with methyl and two fluoro;

30

➤ a group -**L²**-**Ar³**, wherein

- **L²** represents a $-(C_{1-4})$ alkylene-; $-(C_{3-5})$ cycloalkylene- wherein said (C_{3-5}) cycloalkylene optionally contains one ring oxygen atom; $^{*}-(C_{3-5})$ cycloalkylene- (C_{1-2}) alkylene- wherein said (C_{3-5}) cycloalkylene optionally contains one ring oxygen atom, wherein the asterisk indicates the bond to which **Ar³** is attached; $^{*}-(C_{1-2})$ alkylene- (C_{3-5}) cycloalkylene- wherein said (C_{3-5}) cycloalkylene optionally contains one ring oxygen atom, wherein the asterisk indicates the bond to which **Ar³** is attached; or $-(C_{1-3})$ alkylene- which is mono-substituted with hydroxy or trifluoromethyl; and
- **Ar³** represents phenyl, or 5-membered heteroaryl containing one oxygen atom and one or two nitrogen atoms, or 6-membered heteroaryl containing one or two nitrogen atoms; wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C_{1-4}) alkyl, (C_{1-4}) alkoxy, halogen, (C_{1-3}) fluoroalkyl, or (C_{1-3}) fluoroalkoxy; wherein, in case **Ar³** represents 6-membered heteroaryl which is pyridyl or pyrimidinyl, such pyridyl or pyrimidinyl may additionally be present in form of the respective N-oxide;

and **R^{N2}** independently represents hydrogen, or (C_{1-4}) alkyl;

or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 5; wherein

R¹ represents **R^{N1}R^{N2}N-**, wherein

- **R^{N1}** represents

- (C_{3-6}) cycloalkyl, wherein said (C_{3-6}) cycloalkyl optionally contains one ring oxygen atom; wherein said (C_{3-6}) cycloalkyl independently is unsubstituted, or mono-substituted with fluoro, methyl, or hydroxy, or di-substituted with fluoro, or tri-substituted with methyl and two fluoro;
- (C_{3-6}) cycloalkyl- (C_{1-3}) alkylene-, wherein said (C_{3-6}) cycloalkyl optionally contains one ring oxygen atom;
- (C_{3-6}) cycloalkyl- (C_{3-5}) cycloalkylene-;
- phenyl- (C_{1-4}) alkylene- wherein said phenyl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C_{1-4}) alkyl, (C_{1-4}) alkoxy, halogen, (C_{1-3}) fluoroalkyl, or (C_{1-3}) fluoroalkoxy;;
- phenyl- (C_{1-3}) alkylene- wherein said $-(C_{1-3})$ alkylene- is mono-substituted with hydroxy;

- phenyl-(C₃₋₅)cycloalkylene-; wherein said (C₃₋₅)cycloalkylene optionally contains one ring oxygen atom, and wherein said phenyl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, hydroxy, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy;
- 5 ➤ phenyl-(C₃₋₅)cycloalkylene-(C₁₋₂)alkylene- wherein said (C₃₋₅)cycloalkylene optionally contains one ring oxygen atom, and wherein said phenyl is unsubstituted, or mono-substituted with halogen;
- phenyl-(C₁₋₂)alkylene-(C₃₋₅)cycloalkylene- wherein said (C₃₋₅)cycloalkylene optionally contains one ring oxygen atom;
- 10 ➤ 5-membered heteroaryl-(C₁₋₃)alkylene-, wherein said 5-membered heteroaryl contains one oxygen atom and one or two nitrogen atoms; and wherein said 5-membered heteroaryl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy;
- 15 ➤ 6-membered heteroaryl-(C₁₋₄)alkylene-, wherein said 6-membered heteroaryl contains one or two nitrogen atoms; and wherein said 6-membered heteroaryl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; wherein, in case **Ar**³ represents pyridyl or pyrimidinyl, such
- 20 pyridyl or pyrimidinyl may additionally be present in form of the respective N-oxide;
- 6-membered heteroaryl-(C₁₋₃)alkylene-, wherein said -(C₁₋₃)alkylene- is mono-substituted with hydroxy or trifluoromethyl; wherein said 6-membered heteroaryl contains one or two nitrogen atoms; or
- 25 ➤ 6-membered heteroaryl-(C₃₋₅)cycloalkylene-, wherein said 6-membered heteroaryl contains one or two nitrogen atoms; and wherein said 6-membered heteroaryl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; wherein, in case **Ar**³ represents pyridyl or pyrimidinyl, such
- 30 pyridyl or pyrimidinyl may additionally be present in form of the respective N-oxide;
- 6-membered heteroaryl-(C₃₋₅)cycloalkylene-(C₁₋₂)alkylene- wherein said 6-membered heteroaryl contains one or two nitrogen atoms; and wherein said 6-membered heteroaryl is unsubstituted;
- 35 and **R**^{N2} independently represents hydrogen, or (C₁₋₄)alkyl;
- or **R**^{N1} represents (C₁₋₃)alkyl; and **R**^{N2} represents hydrogen, or methyl;

or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 5; wherein R^1 represents $R^{N1}R^{N2}N-$, wherein

• R^{N1} represents

- 5 ➤ (C₃₋₆)cycloalkyl-(C₁₋₃)alkylene-, wherein said (C₃₋₆)cycloalkyl optionally contains one ring oxygen atom;
- phenyl-(C₁₋₄)alkylene- wherein said phenyl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy;
- 10 ➤ phenyl-(C₃₋₅)cycloalkylene- wherein said (C₃₋₅)cycloalkylene optionally contains one ring oxygen atom, and wherein said phenyl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, hydroxy, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy;
- 6-membered heteroaryl-(C₁₋₄)alkylene-, wherein said 6-membered heteroaryl contains one or two nitrogen atoms; and wherein said 6-membered heteroaryl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; wherein, in case Ar^3 represents pyridyl or pyrimidinyl, such pyridyl or pyrimidinyl may additionally be present in form of the respective N-oxide;
- 15 ➤ 6-membered heteroaryl-(C₃₋₅)cycloalkylene-, wherein said 6-membered heteroaryl contains one or two nitrogen atoms; and wherein said 6-membered heteroaryl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; wherein, in case Ar^3 represents pyridyl or pyrimidinyl, such pyridyl or pyrimidinyl may additionally be present in form of the respective N-oxide;
- 20 ➤ 6-membered heteroaryl-(C₃₋₅)cycloalkylene-, wherein said 6-membered heteroaryl contains one or two nitrogen atoms; and wherein said 6-membered heteroaryl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; wherein, in case Ar^3 represents pyridyl or pyrimidinyl, such pyridyl or pyrimidinyl may additionally be present in form of the respective N-oxide;
- 25 ➤ 6-membered heteroaryl-(C₃₋₅)cycloalkylene-, wherein said 6-membered heteroaryl contains one or two nitrogen atoms; and wherein said 6-membered heteroaryl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; wherein, in case Ar^3 represents pyridyl or pyrimidinyl, such pyridyl or pyrimidinyl may additionally be present in form of the respective N-oxide;

and R^{N2} independently represents hydrogen, or (C₁₋₄)alkyl;

or a pharmaceutically acceptable salt thereof.

30 9. A compound according to any one of claims 1 to 5; wherein R^1 represents $R^{N1}R^{N2}N-$, wherein

• R^{N1} represents

- 6-membered heteroaryl-(C₁₋₄)alkylene-, wherein said 6-membered heteroaryl contains one or two nitrogen atoms; and wherein said 6-membered heteroaryl is unsubstituted, or mono-, or di-substituted; wherein the substituents are

independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; wherein, in case **Ar**³ represents pyridyl or pyrimidinyl, such pyridyl or pyrimidinyl may additionally be present in form of the respective N-oxide;

- 5 ➤ 6-membered heteroaryl-(C₃₋₅)cycloalkylene-, wherein said 6-membered heteroaryl contains one or two nitrogen atoms; and wherein said 6-membered heteroaryl is unsubstituted, or mono-, or di-substituted; wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy; wherein, in case **Ar**³ represents pyridyl or pyrimidinyl, such
10 pyridyl or pyrimidinyl may additionally be present in form of the respective N-oxide;

and **R**^{N2} independently represents hydrogen or methyl.

or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of claims 1 to 9; wherein **R**² represents

- 15 • (C₃₋₈)cycloalkyl-(C₁₋₃)alkyl, wherein the (C₃₋₈)cycloalkyl is unsubstituted; or mono-substituted wherein the substituent is (C₁₋₃)alkyl, fluoro, or (C₁₋₃)fluoroalkyl; or di-substituted with fluoro; or
 • (C₃₋₈)cycloalkyl, wherein the (C₃₋₈)cycloalkyl is unsubstituted, or mono- or di-substituted wherein the substituents are independently selected from (C₁₋₃)alkyl, or fluoro;

20 or a pharmaceutically acceptable salt thereof.

11. A compound according to any one of claims 1 to 9; wherein **R**² represents

- unsubstituted (C₃₋₈)cycloalkyl-(C₁₋₃)alkyl; or
 • unsubstituted (C₃₋₆)cycloalkyl; or
 • (C₃₋₈)cycloalkyl, wherein the (C₃₋₈)cycloalkyl is di-substituted with fluoro; or
25 • (C₃₋₈)cycloalkyl-(C₁₋₃)alkyl; wherein the (C₃₋₈)cycloalkyl is mono-substituted with methyl, fluoro, or (C₁)fluoroalkyl; or di-substituted with fluoro;

or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 1 which is:

- (3S,4S)-1-Cyclobutyl-4-[[5-(2,4-difluoro-phenyl)-[1,3,4]thiadiazole-2-carbonyl]-amino]-piperidine-3-carboxylic acid
30 (1-pyrimidin-2-yl-cyclopropyl)-amide;
 (3S,4S)-4-[[5-(2,4-difluoro-phenyl)-[1,3,4]thiadiazole-2-carbonyl]-amino]-1-(1-fluoro-cyclopropylmethyl)-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide;
 or

(3S,4S)-1-Cyclopropylmethyl-4-{{5-(2,4-difluoro-phenyl)-[1,3,4]thiadiazole-2-carbonyl}-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide;

or a pharmaceutically acceptable salt thereof.

- 5 **13.** The compound according to claim 1, which is (3S,4S)-1-Cyclopropylmethyl-4-{{5-(2,4-difluoro-phenyl)-[1,3,4]thiadiazole-2-carbonyl}-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide; or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising, as active principle, one or more compounds according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

- 10 **15.** A compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, for use as a medicament.

16. A compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, for use in the prevention or treatment of cancer, autoimmune disorders, inflammatory diseases, transplant rejection, or fibrosis.

- 15 **17.** Use of a compound of formula (I) as defined in claim 1, or of a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the prevention or treatment of cancer, autoimmune disorders, inflammatory diseases, transplant rejection, or fibrosis.