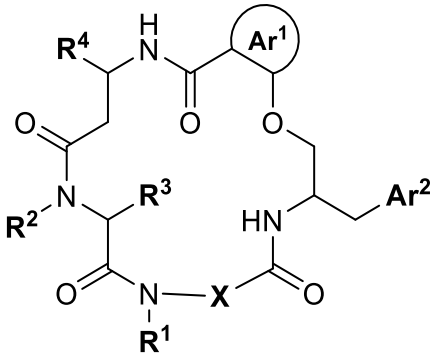
Claims

1. A compound of Formula (I)

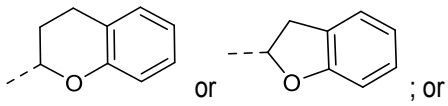


Formula (I)

wherein

- **X** represents -C$R^{X1}R^{X2}$, wherein
  - R^{X1} and R^{X2} together with the carbon atom to which they are attached form a ring which is:
    - C_{3-6}-cycloalkan-1,1-diyl;
    - C_{5-6}-cycloalkan-1,1-diyl which is fused to a benzene ring;
    - C_{3-6}-cycloalkan-1,1-diyl, wherein said C_{3-6}-cycloalkan-1,1-diyl group independently is mono-substituted with C_{1-3}-alkoxy, fluoro, or hydroxy; or di-substituted with fluoro;
    - C_{4-6}-heterocycloalkan-diyl, wherein said C_{4-6}-heterocycloalkan-diyl contains one ring nitrogen atom, wherein said nitrogen when having a free valency is unsubstituted or mono-substituted wherein the substitutents are independently selected from C_{1-4}-alkyl, and -COO-C_{1-3}-alkyl; or
    - C_{4-6}-heterocycloalkan-diyl, wherein said C_{4-6}-heterocycloalkan-diyl contains one ring oxygen atom;
  - R^{X1} and R^{X2} both independently represent C_{1-4}-alkyl; or
  - R^{X1} represents hydrogen, and
    R^{X2} represents
    - hydrogen;
    - C_{1-6}-alkyl;
    - C_{1-4}-fluoroalkyl;
    - C_{3-6}-cycloalkyl;
    - C_{1-3}-alkyl wherein said C_{1-3}-alkyl is mono-substituted with
      - hydroxy;
      - C_{1-4}-alkoxy;

- $-L^{X1}-C_{3-6}$-cycloalkyl wherein said C_{3-6}-cycloalkyl is unsubstituted or di-substituted with fluoro; and wherein L^{X1} independently represents a direct bond or oxygen;
- C_{4-6}-heterocycloalkyl wherein said C_{4-6}-heterocycloalkyl contains one ring oxygen atom;
- $-NR^{N1}R^{N2}$ wherein R^{N1} and R^{N2} together with the nitrogen form a 4- to 6-membered carbocyclic ring comprising the nitrogen atom, wherein said ring is mono- or di-substituted with fluoro;
- a partially aromatic bicyclic ring, which is



; or

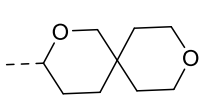
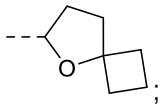
- $-L^{X2}-Ar^{X2}$ wherein -
  - L^{X2} independently represents a direct bond, C_{1-3}-alkylene, $-C_{1-3}$-alkylene-O-*, or $-C_{1-3}$-alkylene-O-C_{1-2}-alkylene-*; wherein the asterisks indicate the bond that is attached to the group Ar^{X2}; and
  - Ar^{X2} independently represents aryl, or 5- to 10-membered heteroaryl; wherein said group Ar^{X2} independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from
    - C_{1-4}-alkyl;
    - C_{1-3}-alkoxy;
    - halogen;
    - C_{3-6}-cycloalkyl;
    - C_{1-3}-fluoroalkyl; and
    - Ar^{X3} wherein Ar^{X3} independently represents phenyl, or 5- or 6-membered heteroaryl; wherein said group Ar^{X3} independently is unsubstituted, or mono-, or di-substituted wherein the substituents independently are selected from C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkoxy-C_{2-3}-alkyl, C_{3-5}-cycloalkyl, C_{1-3}-fluoroalkyl, and halogen;

and

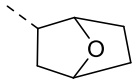
R^1 independently represents

- hydrogen;
- $-C_{1-8}$-alkyl;
- $-C_{2-6}$-alkyl wherein said C_{2-6}-alkyl is mono-substituted with hydroxy, or C_{1-4}-alkoxy;
- $-C_{1-6}$-alkyl wherein said C_{1-6}-alkyl is mono-substituted with R^{11}; wherein R^{11} independently represents

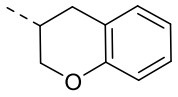
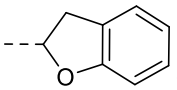
- a saturated 5- or 6-membered heterocycloalkyl containing one or two ring heteroatoms wherein said heteroatoms are independently selected from nitrogen and oxygen, wherein said 5- or 6-membered heterocycloalkyl is independently unsubstituted, mono- or di-substituted, wherein the substituents independently are selected from C_{1-4}-alkyl, halogen, and benzyl;
- C_{3-6}-cycloalkyl, wherein said C_{3-6}-cycloalkyl is unsubstituted or mono-substituted with C_{1-4}-alkoxy;
- phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is is unsubstituted, mono- or di-substituted wherein the substitutents independently are selected from C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, halogen, cyano, and morpholin-4-yl;
- benzyloxy;
- a spirocyclic fragment, which is

 or ;

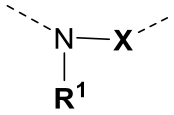
- a saturated bicyclic ring, which is

; or

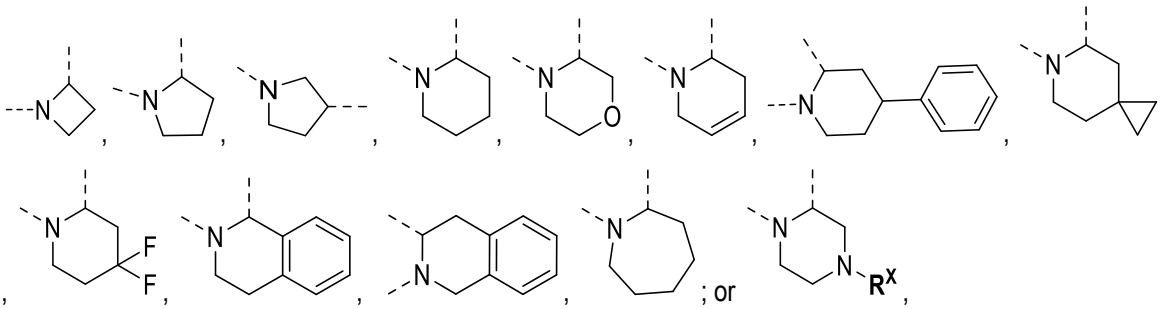
- a partially aromatic bicyclic ring, which is

 or ;

❖ or the fragment

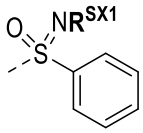


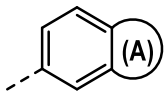
represents a heterocyclic ring which is



wherein $\mathbf{R^x}$ represents

- hydrogen;

- C_{1-4}-alkyl;
- C_{3-6}-cycloalkyl;
- C_{1-4}-alkyl, wherein said C_{1-4}-alkyl is mono-substituted with C_{3-4}-cycloalkyl;
- C_{2-4}-alkyl, wherein said C_{2-4}-alkyl is mono-substituted with hydroxy or C_{1-3}-alkoxy;
- phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C_{1-4}-alkyl, C_{1-3}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, cyano or halogen;
- , wherein $\mathbf{R^{SX1}}$ represents hydrogen or -CO-O-C_{1-4}-alkyl;
- -CO-$\mathbf{R^{OX1}}$, or -SO_2-$\mathbf{R^{OX1}}$; wherein $\mathbf{R^{OX1}}$ independently represents
  - C_{1-4}-alkyl;
  - C_{1-3}-alkyl wherein said C_{1-3}-alkyl is mono-substituted with C_{1-3}-alkoxy, tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl, or -N$\mathbf{R^{ONX1}}\mathbf{R^{ONX2}}$ wherein $\mathbf{R^{ONX1}}$ and $\mathbf{R^{ONX2}}$ independently represent hydrogen or C_{1-3}-alkyl;
  - tetrahydropyranyl;
  - phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C_{1-4}-alkyl, C_{1-3}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, cyano or halogen; or
  - a group of the structure (R^{X-A}):



(R^{X-A})

wherein (A) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (A) comprises two heteroatoms independently selected from oxygen and nitrogen; wherein said ring (A) independently is unsubstituted or mono-substituted wherein the substitutents independently are selected from oxo and C_{1-3}-alkyl; or

- -CO-O-$\mathbf{R^{OX2}}$; wherein $\mathbf{R^{OX2}}$ represents
  - C_{1-4}-alkyl;
  - 2,2,2-trichloroethyl; or
  - tetrahydropyranyl;

$\mathbf{R^2}$ represents C_{1-4}-alkyl;

$\mathbf{R^3}$ represents hydrogen; C_{1-6}-alkyl; -CH_2-C_{3-6}-cycloalkyl; or C_{2-4}-alkynyl;

R^4 represents a group -CO-NH-**R^{41}**; wherein **R^{41}** represents

- C_{2-6}-alkyl, which is mono-substituted with C_{1-4}-alkoxy, C_{1-4}-fluoroalkoxy, or hydroxy;
- C_{1-3}-alkoxy-C_{2-3}-alkylene-O-CH_2-CH_2-;
- -CH_2-CH_2-C_{5-6}-heterocycloalkyl, wherein said C_{5-6}-heterocycloalkyl contains one ring oxygen atom, wherein said C_{5-6}-heterocyclyl is unsubstituted, mono- or di-substituted with C_{1-4}-alkyl;
- **-L^1-**aryl; wherein **L^1** represents -CH_2-CH_2-, -CH_2-CH_2-O-*, -CH_2-CF_2-*, -CH_2-(cyclopropan-1,1-diyl)-*, -CH(CH_2-OH)-CH_2-*, or -CH_2-CH(OH)-*; wherein asterisks indicate the bond with which **L^1** is attached to the aryl; wherein aryl represents phenyl or naphthyl; wherein said aryl is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, halogen, cyano, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-methyl, C_{1-3}-alkoxy-C_{1-3}-alkyl, hydroxy-C_{1-3}-alkyl, C_{2-3}-alkynyl, morpholin-4-yl, C_{1-3}-alkyl-SO_2-, 5- or 6-membered heteroaryl, or -N**R^{N41}****R^{N42}**, wherein independently **R^{N41}** is hydrogen or C_{1-4}-alkyl, and **R^{N42}** is hydrogen or C_{1-4}-alkyl;
- **-L^2-HET**; wherein **L^2** represents -CH_2-CH_2-, -CH_2-CH_2-O-*, -CH_2-CF_2-*, -CH_2-(cyclopropan-1,1-diyl)-*, -CH(CH_2-OH)-CH_2-*, or -CH_2-CH(OH)-*; wherein asterisks indicate the bond with which **L^2** is attached to **HET**; wherein **HET** represents 5- to 10-membered heteroaryl, wherein said **HET** is independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C_{1-4}-alkyl; C_{1-4}-alkoxy; C_{1-3}-fluoroalkyl; C_{1-3}-fluoroalkoxy; halogen; cyano; C_{3-6}-cycloalkyl; C_{3-6}-cycloalkyl-methyl; C_{1-3}-alkoxy-C_{1-3}-alkyl; hydroxy-C_{1-3}-alkyl; C_{2-3}-alkynyl; benzyl; or phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are C_{1-4}-alkyl, C_{1-4}-alkoxy, or C_{1-4}-fluoroalkoxy;
- -CH_2-CH_2-**HCy^1**, wherein **HCy^1** represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one or two heteroatoms independently selected from oxygen and nitrogen, wherein, if present, said nitrogen when having a free valency is unsubstituted or mono-substituted with C_{1-4}-alkyl; and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are indepently C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, halogen, or cyano;
- -CH_2-CH_2-**HCy^2**, wherein **HCy^2** represents a partially aromatic bicyclic ring system consisting of a 5-membered heteroaryl which is fused to a 5- to 7-membered saturated carbocyclic ring; or
- **-L^3-HCy^3**, wherein **L^3** represents a direct bond, or -CH_2-; wherein **HCy^3** represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one oxygen atom; wherein **L^3** is attached to said group **HCy^3** at a carbon atom which is part of said 5- to 7-membered saturated heterocyclic ring; and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, or mono-substituted with C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, halogen, or cyano;

Ar^1 represents

- 5- or 6-membered heteroarylene wherein said 5- or 6-membered heteroarylene is unsubstituted;

- phenylene, or 5- or 6-membered heteroarylene; wherein said phenylene, or 5- or 6-membered heteroarylene independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, cyano, and halogen;
- phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, wherein said 5- or 6-membered saturated heterocyclic ring independently is unsubstituted or di-substituted with fluoro; or
- a bicyclic aromatic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene; wherein said bicyclic aromatic ring independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from C_{1-4}-alkyl, C_{1-3}-fluoroalkyl, C_{1-4}-alkoxy, C_{1-3}-fluoroalkoxy, cyano, and halogen; or
- quinoline-diyl, wherein said quinoline-diyl is present in form of the respective N-oxide; wherein said quinoline-diyl N-oxide is unsubstituted, or said quinoline-diyl N-oxide is mono-substituted with methyl or fluoro;

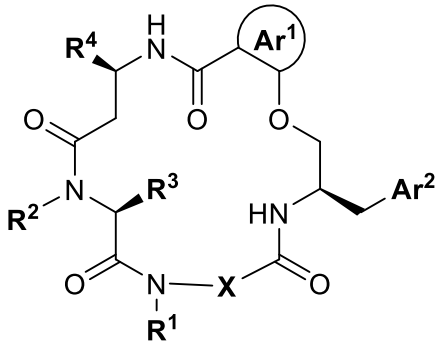
and

Ar^2 represents

- phenyl or naphthyl, wherein said phenyl or naphthyl independently is unsubstituted, mono- or di-substituted wherein the substituents are independently selected from C_{1-4}-alkyl, C_{1-3}-fluoroalkyl, halogen, cyano, C_{1-6}-alkoxy, and C_{1-3}-fluoroalkoxy;
- 5- or 6-membered heteroaryl, wherein said 5- or 6-membered heteroaryl independently is unsubstituted or mono-substituted wherein the substituents are independently selected from C_{1-4}-alkyl, C_{1-3}-fluoroalkyl, halogen, cyano, C_{1-6}-alkoxy, and C_{1-3}-fluoroalkoxy; or
- 9- or 10-membered heteroaryl;

or a pharmaceutically acceptable salt thereof.

2. A compound of Formula (I) as defined for claim 1, wherein the compounds are also compounds of Formula (I_E):



Formula (I_E);

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2; wherein

- **X** represents -C$\mathbf{R^{X1}R^{X2}}$, wherein
  - $\mathbf{R^{X1}}$ and $\mathbf{R^{X2}}$ together with the carbon atom to which they are attached form a ring which is:
    - C_{3-6}-cycloalkan-1,1-diyl-;
    - C_{5-6}-cycloalkan-1,1-diyl- which is fused to a benzene ring; or
    - C_{3-6}-cycloalkan-1,1-diyl-, wherein said C_{3-6}-cycloalkan-1,1-diyl group is mono-substituted with C_{1-3}-alkoxy, or di-substituted with fluoro;
  - $\mathbf{R^{X1}}$ and $\mathbf{R^{X2}}$ both independently represent C_{1-4}-alkyl; or
  - $\mathbf{R^{X1}}$ represents hydrogen, and

    $\mathbf{R^{X2}}$ represents
    - hydrogen;
    - C_{1-6}-alkyl;
    - C_{1-4}-fluoroalkyl;
    - C_{3-6}-cycloalkyl;
    - C_{1-3}-alkyl wherein said C_{1-3}-alkyl is mono-substituted with
      - hydroxy;
      - C_{1-4}-alkoxy;
      - -$\mathbf{L^{X1}}$-C_{3-6}-cycloalkyl wherein said C_{3-6}-cycloalkyl is unsubstituted or di-substituted with fluoro; and wherein $\mathbf{L^{X1}}$ independently represents a direct bond or oxygen;
      - C_{4-6}-heterocycloalkyl wherein said C_{4-6}-heterocycloalkyl contains one ring oxygen atom;
      - -N$\mathbf{R^{N1}R^{N2}}$ wherein $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ together with the nitrogen form a 4- to 6-membered carbocyclic ring comprising the nitrogen atom, wherein said ring is mono- or di-substituted with fluoro;
    - -$\mathbf{L^{X2}}$-$\mathbf{Ar^{X2}}$ wherein -
      - $\mathbf{L^{X2}}$ independently represents a direct bond, C_{1-3}-alkylene, -C_{1-3}-alkylene-O-*, or -C_{1-3}-alkylene-O-C_{1-2}-alkylene-*; wherein the asterisks indicate the bond that is attached to the group $\mathbf{Ar^{X2}}$; and
      - $\mathbf{Ar^{X2}}$ independently represents aryl, or 5- to 10-membered heteroaryl; wherein said group $\mathbf{Ar^{X2}}$ independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from
        - C_{1-4}-alkyl;
        - C_{1-3}-alkoxy;
        - halogen;
        - cyano;

- C_{3-6}-cycloalkyl;
- C_{1-3}-fluoroalkyl; and
- Ar^{X3} wherein Ar^{X3} independently represents phenyl, or 5- or 6-membered heteroaryl; wherein said group Ar^{X3} independently is unsubstituted, or mono-, or di-substituted wherein the substituents independently are selected from C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkoxy-C_{2-3}-alkyl, C_{3-5}-cycloalkyl, C_{1-3}-fluoroalkyl, and halogen;

and

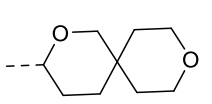
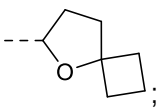
R^1 independently represents hydrogen or -C_{1-3}-alkyl; or

- **X** represents -$CR^{X1}R^{X2}$, wherein
  - R^{X1} represents hydrogen, and
    R^{X2} represents hydrogen, or methyl; or
  - R^{X1} and R^{X2} together with the carbon atom to which they are attached form a ring which is C_{3-5}-cycloalkan-1,1-diyl-;

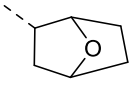
and

R^1 independently represents

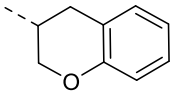
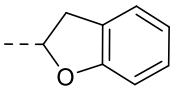
- -C_{4-6}-alkyl;
- -C_{2-6}-alkyl, wherein said C_{2-6}-alkyl is mono-substituted with C_{1-4}-alkoxy;
- -C_{3-6}-alkyl, wherein said C_{3-6}-alkyl is mono-substituted with phenyl, or benzyloxy;
- -$(CH_2)_m$-R^{11} wherein **m** represents the integer 1 or 2; and R^{11} independently represents
  - a saturated 5- or 6-membered heterocycloalkyl containing one or two ring oxygen atoms, wherein said 5- or 6-membered heterocycloalkyl is independently unsubstituted, mono- or di-substituted with C_{1-4}-alkyl;
  - C_{3-6}-cycloalkyl, wherein said C_{3-6}-cycloalkyl is unsubstituted or mono-substituted with C_{1-4}-alkoxy;
  - phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, cyano or halogen;
  - a spirocyclic fragment, which is


or

;

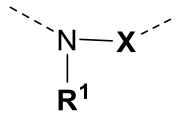
  - a saturated bicyclic ring, which is


; or

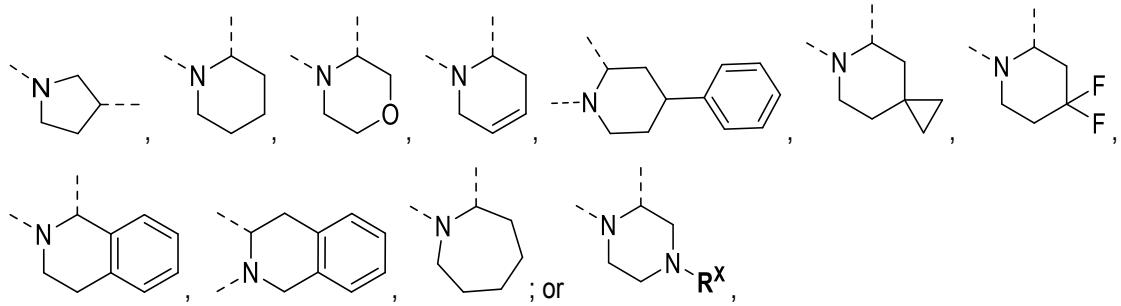
- a partially aromatic bicyclic ring, which is

 or ;

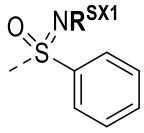
- or the fragment



represents a heterocyclic ring which is

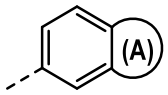


wherein $\mathbf{R^X}$ represents

- hydrogen;
- C_{1-4}-alkyl;
- C_{3-4}-cycloalkyl;
- C_{1-4}-alkyl, wherein said C_{1-4}-alkyl is mono-substituted with C_{3-4}-cycloalkyl;
- C_{2-4}-alkyl, wherein said C_{2-4}-alkyl is mono-substituted with hydroxy, or C_{1-3}-alkoxy;
- phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C_{1-4}-alkyl, C_{1-3}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, cyano or halogen;
- , wherein $\mathbf{R^{SX1}}$ represents hydrogen or -CO-O-C_{1-4}-alkyl;
- -CO-$\mathbf{R^{OX1}}$, or -SO_2-$\mathbf{R^{OX1}}$; wherein $\mathbf{R^{OX1}}$ independently represents
  - C_{1-4}-alkyl;
  - C_{1-3}-alkyl wherein said C_{1-3}-alkyl is mono-substituted with C_{1-3}-alkoxy, tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl, or -N$\mathbf{R^{ONX1}R^{ONX2}}$ wherein $\mathbf{R^{ONX1}}$ and $\mathbf{R^{ONX2}}$ independently represent hydrogen or C_{1-3}-alkyl;
  - tetrahydropyranyl;
  - phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the

substituents independently are selected from C_{1-4}-alkyl, C_{1-3}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, cyano or halogen; or

- a group of the structure (R^{X-A}):



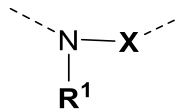
(R^{X-A})

wherein (A) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (A) comprises two heteroatoms independently selected from oxygen and nitrogen; wherein said ring (A) independently is unsubstituted or mono-substituted wherein the substitutents independently are selected from oxo and C_{1-3}-alkyl; or

- -CO-O-$\mathbf{R^{OX2}}$; wherein $\mathbf{R^{OX2}}$ represents
  - C_{1-4}-alkyl;
  - 2,2,2-trichloroethyl; or
  - tetrahydropyranyl;

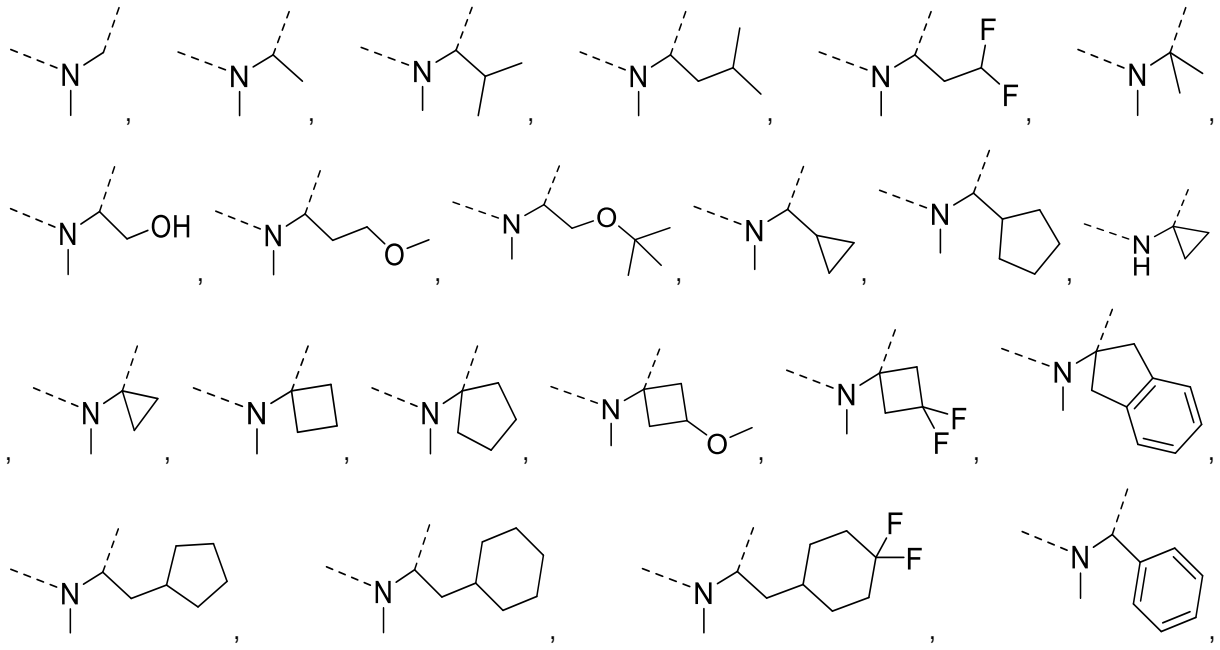
or a pharmaceutically acceptable salt thereof.

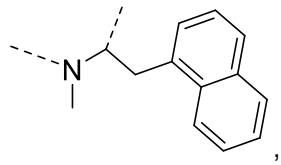
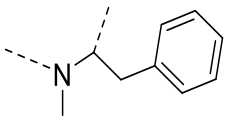
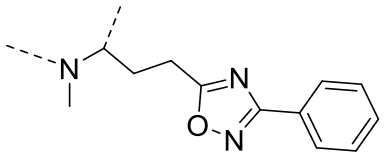
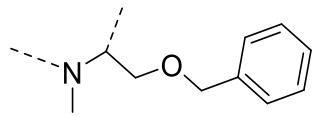
4. A compound according to claim 1 or 2; wherein the fragment



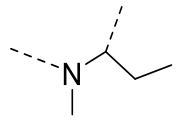
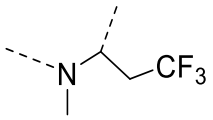
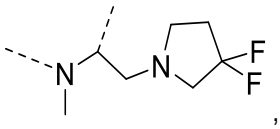
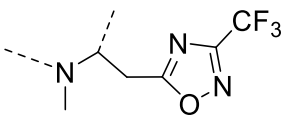
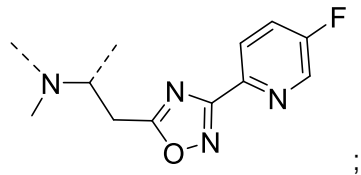
represents a group selected from:

A)

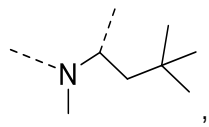
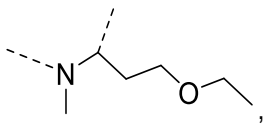
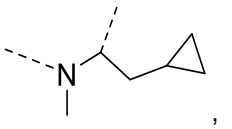
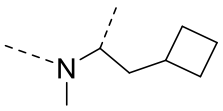
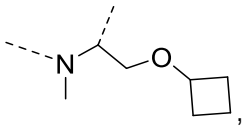
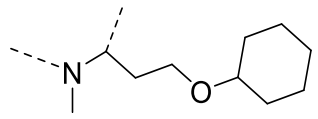
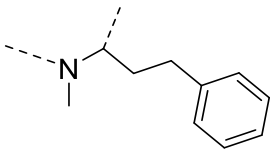
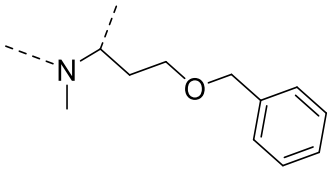
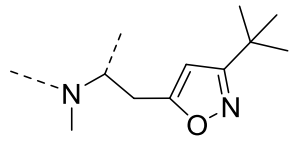
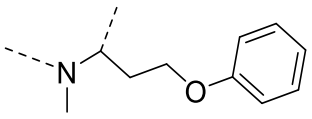
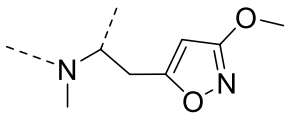
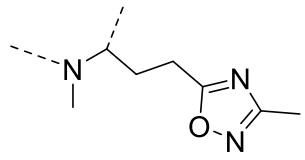
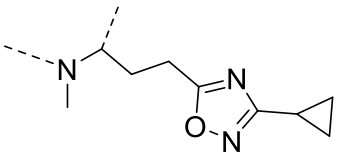
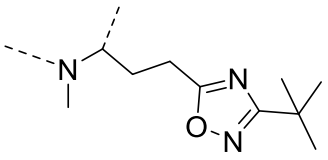
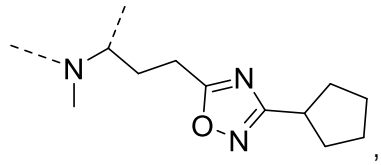
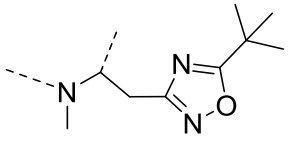
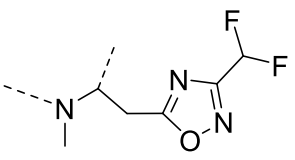
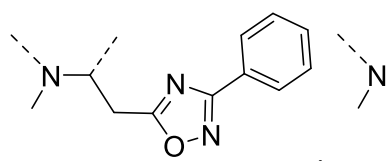
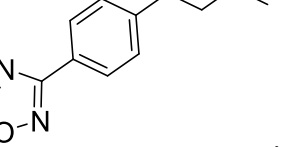
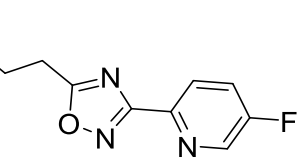



,

,

, or

;

B)


,

,

,

, or

;

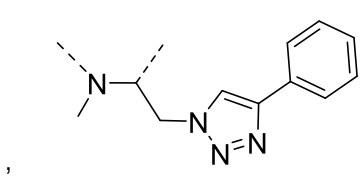
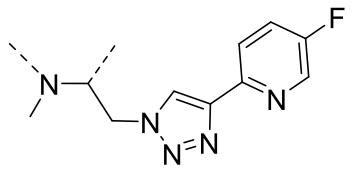
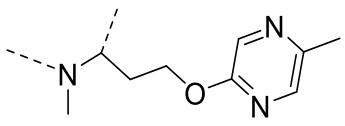
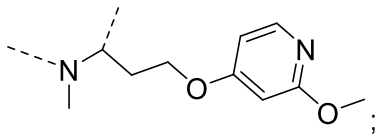
C)


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

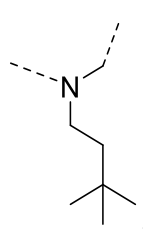
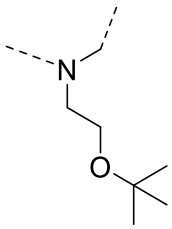
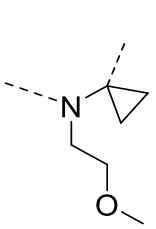
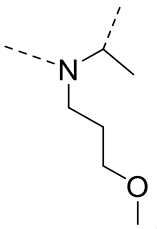
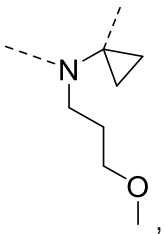
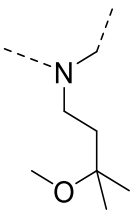
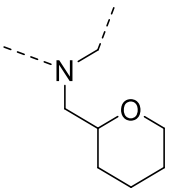
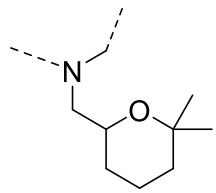
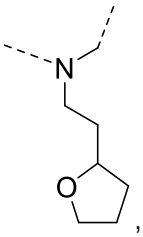
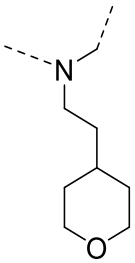
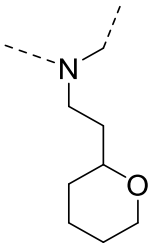
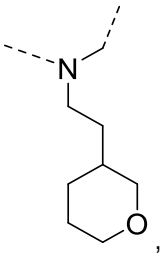
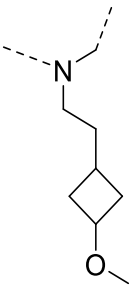
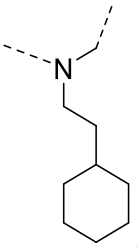
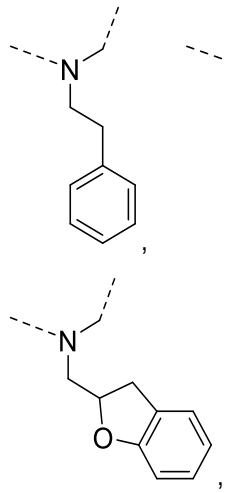
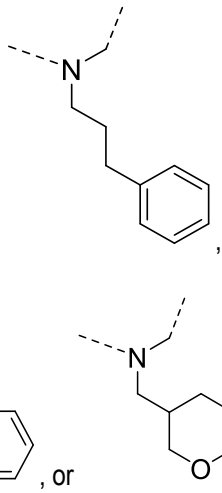
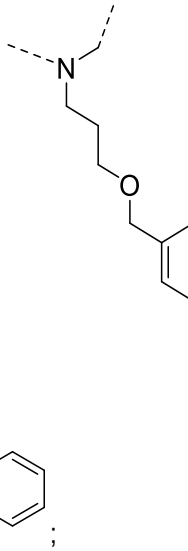
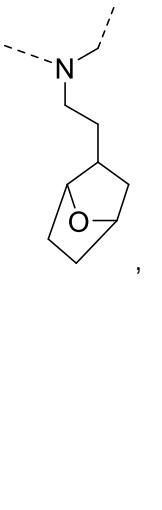
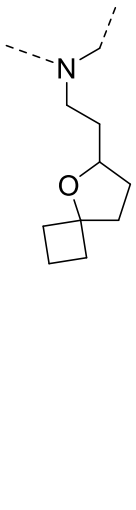
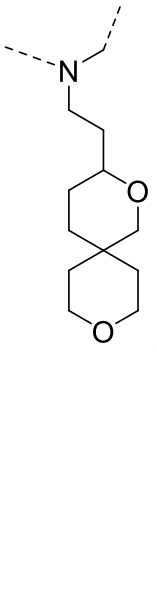
,

,

,


,

,

, or

;

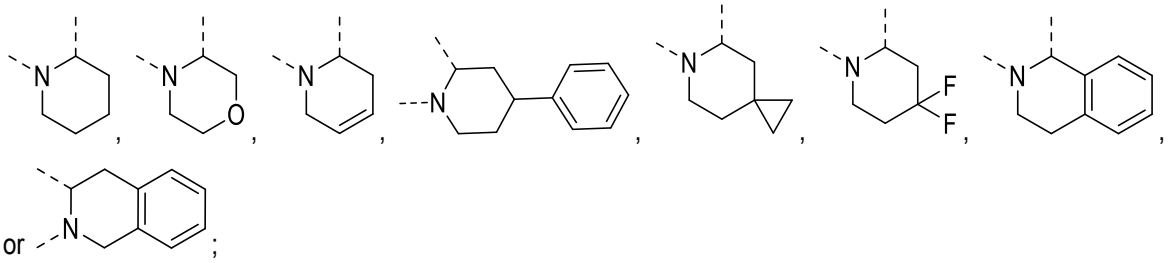
D)


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

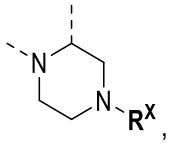
, or

;

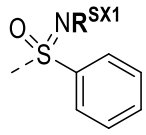
E)

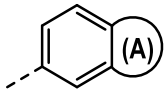


F)



wherein $\mathbf{R^X}$ represents

- C_{1-4}-alkyl;
- C_{3-4}-cycloalkyl;
- C_{1-4}-alkyl, wherein said C_{1-4}-alkyl is mono-substituted with C_{3-4}-cycloalkyl;
- C_{1-4}-alkyl, wherein said C_{1-4}-alkyl is mono-substituted with hydroxy, or C_{1-3}-alkoxy;
- phenyl;
- 6-membered heteroaryl, wherein said 6-membered heteroaryl is unsubstituted or mono-substituted with halogen;
- , wherein $\mathbf{R^{SX1}}$ represents -CO-O-C_{1-4}-alkyl;
- -CO-$\mathbf{R^{OX1}}$, or -SO_2-$\mathbf{R^{OX1}}$; wherein $\mathbf{R^{OX1}}$ independently represents
  - C_{1-4}-alkyl;
  - C_{1-3}-alkyl wherein said C_{1-3}-alkyl is mono-substituted with C_{1-3}-alkoxy, tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl, or -N$\mathbf{R^{ONX1}R^{ONX2}}$ wherein $\mathbf{R^{ONX1}}$ and $\mathbf{R^{ONX2}}$ independently represent hydrogen or C_{1-3}-alkyl;
  - tetrahydropyranyl;
  - phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are C_{1-3}-alkoxy, C_{1-3}-fluoroalkoxy or halogen;
  - 5- or 6-membered heteroaryl wherein said 5- or 6-membered heteroaryl is independently unsubstituted or mono-substituted with C_{1-3}-alkoxy; or
  - a group of the structure (R^{X-A}):

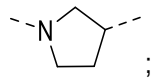


(R^{X-A})

wherein (A) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (A) comprises two heteroatoms independently selected from oxygen and nitrogen; wherein said ring (A) independently is unsubstituted or mono-substituted wherein the substitutents independently are selected from oxo and C_{1-3}-alkyl; or

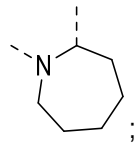
- -CO-O-$\mathbf{R^{OX2}}$; wherein $\mathbf{R^{OX2}}$ represents
  - C_{1-4}-alkyl;
  - 2,2,2-trichloroethyl; or
  - tetrahydropyranyl;

G)



;

or H)



;

or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4; wherein $\mathbf{R^2}$ represents methyl;
or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 5; wherein $\mathbf{R^3}$ represents isobutyl;
or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 6; wherein $\mathbf{R^4}$ represents a group -CO-NH-$\mathbf{R^{41}}$; wherein $\mathbf{R^{41}}$ represents

- C_{2-6}-alkyl, which is mono-substituted with C_{1-4}-alkoxy, or C_{1-4}-fluoroalkoxy;
- C_{1-3}-alkoxy-C_{2-3}-alkylene-O-CH_2-CH_2-;
- -CH_2-CH_2-C_{5-6}-heterocycloalkyl, wherein said C_{5-6}-heterocycloalkyl contains one ring oxygen atom, wherein said C_{5-6}-heterocyclyl is unsubstituted, mono- or di-substituted with C_{1-4}-alkyl;
- -$\mathbf{L^1}$-aryl; wherein $\mathbf{L^1}$ represents -CH_2-CH_2-, -CH_2-CH_2-O-* or -CH_2-CF_2-*, -CH_2-(cyclopropan-1,1-diyl)-*, -CH(CH_2-OH)-CH_2-*, or -CH_2-CH(OH)-*; wherein asterisks indicate the bond with which $\mathbf{L^1}$ is attached to

the aryl; wherein aryl represents phenyl; wherein said aryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, halogen, cyano, hydroxy-C_{1-3}-alkyl, C_{2-3}-alkynyl, morpholin-4-yl, C_{1-3}-alkyl-SO_2-, 5- or 6-membered heteroaryl, or -N$\mathbf{R^{N41}R^{N42}}$, wherein independently $\mathbf{R^{N41}}$ is hydrogen or C_{1-4}-alkyl, and $\mathbf{R^{N42}}$ is hydrogen or C_{1-4}-alkyl;

- -$\mathbf{L^2}$-$\mathbf{HET^1}$; wherein $\mathbf{L^2}$ represents -CH_2-CH_2-, -CH_2-CF_2-*, -CH_2-(cyclopropan-1,1-diyl)-*, or -CH_2-CH(OH)-*; wherein asterisks indicate the bond with which $\mathbf{L^2}$ is attached to $\mathbf{HET^1}$; wherein $\mathbf{HET^1}$ represents 5- or 6-membered heteroaryl, wherein said 5- or 6-membered heteroaryl is independently unsubstituted, mono-, or di-substituted, wherein the substituents are independently C_{1-4}-alkyl; C_{1-4}-alkoxy; C_{1-3}-fluoroalkyl; halogen; C_{3-6}-cycloalkyl; C_{3-6}-cycloalkyl-methyl; C_{1-3}-alkoxy-C_{1-3}-alkyl; C_{2-3}-alkynyl, benzyl; or phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are C_{1-4}-alkyl, C_{1-4}-alkoxy, or C_{1-4}-fluoroalkoxy;
- -CH_2-CH_2-$\mathbf{HET^2}$, wherein $\mathbf{HET^2}$ represents 9- or 10-membered bicyclic heteroaryl, wherein said $\mathbf{HET^2}$ is unsubstituted;
- -CH_2-CH_2-$\mathbf{HCy^1}$, wherein $\mathbf{HCy^1}$ represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one or two heteroatoms independently selected from oxygen and nitrogen, wherein, if present, said nitrogen when having a free valency is unsubstituted or mono-substituted with C_{1-4}-alkyl; and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, mono-, or di-substituted, wherein the substituents are indepently C_{1-4}-alkyl, C_{1-4}-alkoxy, or halogen; or
- -CH_2-CH_2-$\mathbf{HCy^2}$, wherein $\mathbf{HCy^2}$ represents a partially aromatic bicyclic ring system consisting of a 5-membered heteroaryl which is fused to a 5- to 7-membered saturated carbocyclic ring;

or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 7; wherein $\mathbf{Ar^2}$ represents phenyl;
or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8, wherein $\mathbf{Ar^1}$ represents

- phenylene, or 5- or 6-membered heteroarylene; wherein said phenylene, or 5- or 6-membered heteroarylene independently is mono-, or di-substituted, wherein the substituents are independently selected from C_{1-4}-alkyl, C_{1-4}-alkoxy, and halogen;
- phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, wherein said 5- or 6-membered saturated heterocyclic ring independently is unsubstituted; or

- a bicyclic aromatic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene; wherein said bicyclic aromatic ring independently is unsubstituted, or mono-substituted, wherein the substituents are independently selected from C_{1-4}-alkyl, and halogen;

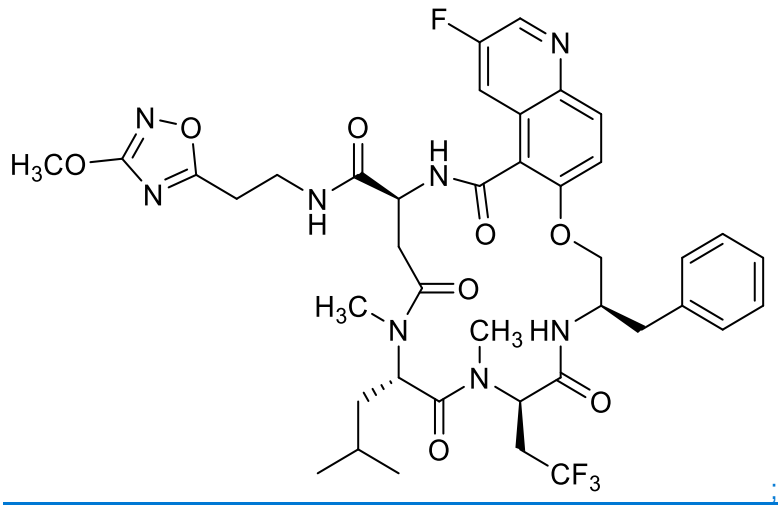
or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 wherein said compound is the compound of example 1; 2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66; 67; 68; 69; 70; 71; 72; 73; 74; 75; 76; 77; 78; 79; 80; 81; 82; 83; 84; 85; 86; 87; 88; 89; 90; 91; 92; 93; 94; 95; 96; 97; 98; 99; 100; 101; 102; 103; 104; 105; 106; 107; 108; 109; 110; 111; 112; 113; 114; 115; 116; 117; 118; 119; 120; 121; 122; 123; 124; 125; 126; 127; 128; 129; 130; 131; 132; 133; 134; 135; 136; 137; 138; 139; 140; 141; 142; 143; 144; 145; 146; 147; 148; 149; 150; 151; 152; 153; 154; 155; 156; 157; 158; 159; 160; 161; 162; 163; 164; 165; 166; 167; 168; 169; 170; 171; 172; 173; 174; 175; 176; 177; 178; 179; 180; 181; 182; 183; 184; 185; 186; 187; 188; 189; 190; 191; 192; 193; 194; 195; 196; 197; 198; 199; 200; 201; 202; 203; 204; 205; 206; 207; 208; 209; 210; 211; 212; 213; 214; 215; 216; 217; 218; 219; 220; 221; 222; 223; 224; 225; 226; 227; 228; 229; 230; 231; 232; 233; 234; 235; 236; 237; 238; 239; 240; 241; 242; 243; 244; 245; 246; 247; 248; 249; 250; 251; 252; 253; 254; 255; 256; 257; 258; 259; 260; 261; 262; 263; 264; 265; 266; 267; 268; 269; 270; 271; 272; 273; 274; 275; 276; 277; 278; 279; 280; 281; 282; 283; 284; 285; 286; 287; 288; 289; 290; 291; 292; 293; 294; 295; 296; 297; 298; 299; 300; 301; 302; 303; 304; 305; 306; 307; 308; 309; 310; 311; 312; 313; 314; 315; 316; 317; 318; 319; 320; 321; 322; 323; 324; 325; 326; 327; 328; 329; 330; 331; 332; 333; 334; 335; 336; 337; 338; 339; 340; 341; 342; 343; 344; 345; 346; 347; 348; 349; 350; 351; 352; 353; 354; 355; 356; 357; 358; 359; 360; 361; 362; 363; 364; 365; 366; 367; 368; 369; 370; 371; 372; 373; 374; 375; 376; 377; 378; 379; 380; 381; 382; 383; 384; 385; 386; 387; 388; 389; 390; 391; 392; 393; 394; 395; 396; 397; 398; 399; 400; 401; 402; 403; 404; 405; 406; 407; 408; 409; 410; 411; 412; 413; 414; 415; 416; 417; 418; 419; 420; 421; 422; 423; 424; 425; 426; 427; 428; 429; 430; 431; 432; 433; 434; 435; 436; 437; 438; 439; 440; 441; 442; 443; 444; 445; 446; 447; 448; 449; 450; 451; 452; 453; 454; 455; 456; 457; 458; 459; 460; 461; 462; 463; 464; 465; 466; 467; 468; 469; 470; 471; 472; 473; 474; 475; 476; 477; 478; 479; 480; 481; 482; 483; 484; 485; 486; 487; 488; 489; 490; 491; 492; 493; 494; 495; 496; 497; 498; 499; 500; 501; 502; 503; 504; 505; 506; 507; 508; 509; 510; 511; 512; 513; 514; 515; 516; 517; 518; 519; 520; 521; 522; 523; 524; 525; 526; 527; 528; 529; 530; 531; 532; 533; 534; 535; 536; 537; 538; 539; 540; 541; 542; 543; 544; 545; 546; 547; 548; 549; 550; 551; 552; 553; 554; 555; 556; 557; 558; 559; 560; 561; 562; 563; 564; 565; 566; 567; 568; 569; 570; 571; 572; 573; 574; 575; 576; 577; 578; 579; 580; 581; 582; 583; 584; 585; 586; 587; 588; 589; 590; 591; 592; 593; 594; 595; 596; 597; 598; 599; 600; 601; 602; 603; 604; 605; 606; 607; 608; 609; 610; 611; 612; 613; 614; 615; 616; 617; 618; 619; 620; 621; 622; 623; 624; 625; 626; 627; 628; 629; 630; 631; 632; 633; 634; 635; 636; 637; 638; 639; 640; 641; 642; 643; 644; 645; 646; 647; 648; 649; 650; 651; 652; 653; 654; 655; 656; 657; 658; 659; 660; 661; 662; 663; 664; 665; 666; 667; 668; 669; 670; 671; 672; 673; 674; 675; 676; 677; 678; 679; 680; 681; 682; 683; 684; 685; 686; 689; 690; 691; 692; 693; 694; 695; 696; 697; 698; 699; 700; 701; 702; 703; 704; 705; 706; 707; 708; 709; 710; 711; 712; 713; 714; 715; 716; 717; 718; 719; 720; 721; 722;

723; 724; 725; 726; 727; 728; 729; 730; 731; 732; 733; 734; 735; 736; 737; 738; 739; 740; 741; 742; 743; 744; 745; 746; 747; 748; 749; 750; 751; 752; 753; 754; 755; 756; 757; 758; 759; 760; 761; 762; 763; 764; 765; 766; 767; 768; 769; 770; 771; 772; 773; 774; 775; 776; 777; 778; 779; 780; 781; 782; 783; 784; 785; 786; 787; 788; 789; 790; 791; 792; 793; 794; 795; 796; 797; 798; 799; 800; 801; 802; 803; 804; 805; 806; 807; 808; 809; 810; 811; 812; 813; 814; 815; 816; 817; 818; 819; 820; 821; 822; 823; 824; 825; 826; 827; 828; 829; 830; 831; 832; 833; 834; 835; 836; 837; 838; 839; 840; 841; 842; 843; 844; 845; 846; 847; 848; 849; 850; 851; 852; 853; 854; 855; 856; 857; 858; 859; 860; 861; 862; 863; 864; 865; 866; 867; 868; 869; 870; 871; 872; 873; 874; 875; 876; 877; 878; 879; 880; 881; 882; 883; 884; 885; 886; 887; 888; 889; 890; 891; 892; 893; 894; 895; 896; 897; 898; 899; 900; 901; 902; 903; 904; 905; 906; 907; 908; 909; 910; 911; 912; 913; 914; 915; 916; 917; 918; 919; 920; 921; 922; 923; 924; 925; 926; 927; 928; 929; 930; 931; 932; 933; 934; 935; 936; 937; 938; 939; 940; 941; 942; 943; 944; 945; 946; 947; 948; 949; 950; 951; 952; 953; 954; 955; 956; 957; 958; 959; 960; 961; 962; 963; 964; 965; 966; 967; 968; 969; 970; 971; 972; 973; 974; 975; 976; 977; 978; 979; 980; 981; 982; or 983;

or a pharmaceutically acceptable salt thereof.

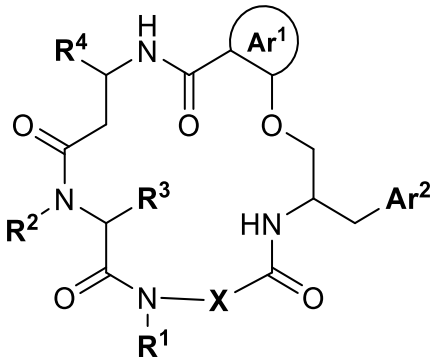
11. A compound according to claim 1, wherein said compound is (3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide:



;

or a pharmaceutically acceptable salt thereof.

~~11~~12. A compound of Formula (II)



Formula (II)

for use in the treatment of cystic fibrosis;

wherein **X**, R^1, R^2, R^3, R^4, Ar^2 are as defined for the compounds of Formula (I) according to claim 1; and

Ar^1 represents

- phenylene wherein said phenylene is unsubstituted;
- 5- or 6-membered heteroarylene wherein said 5- or 6-membered heteroarylene is unsubstituted;
- phenylene, or 5- or 6-membered heteroarylene; wherein said phenylene, or 5- or 6-membered heteroarylene independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-3}-fluoroalkyl, C_{1-3}-fluoroalkoxy, cyano, and halogen;
- phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, wherein said 5- or 6-membered saturated heterocyclic ring independently is unsubstituted or di-substituted with fluoro; or
- a bicyclic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene; wherein said bicyclic ring independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from C_{1-4}-alkyl, C_{1-3}-fluoroalkyl, C_{1-4}-alkoxy, C_{1-3}-fluoroalkoxy, cyano, and halogen; or
- quinoline-diyl, wherein said quinoline-diyl is present in form of the respective N-oxide; wherein said quinoline-diyl N-oxide is unsubstituted, or said quinoline-diyl N-oxide is mono-substituted with methyl or fluoro;

or a pharmaceutically acceptable salt thereof.

~~12~~13. A pharmaceutical composition comprising a compound according to any one of claims 1 to ~~10~~11, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

~~13~~14. A compound according to any one of claims 1 to ~~10~~11, or a pharmaceutically acceptable salt thereof, for use as a medicament.

~~14~~15. A compound according to any one of claims 1 to 11~~10~~, or a pharmaceutically acceptable salt thereof, for use in the treatment of CFTR-related diseases and disorders including cystic fibrosis.

~~15~~16. ~~A method of treatment of CFTR-related diseases and disorders including cystic fibrosis, said method comprising administering to a subject in need thereof an effective amount of~~ Use of a compound according to any one of claims 1 to ~~10~~11, or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating CFTR-related diseases and disorders including cystic fibrosis, wherein an effective amount of the compound is to be administered into a subject in need thereof .