DERIVATIVES OF 6-(6-O-CYCLOALKYL- OR 6-NH-CYCLOALKYL-TRIAZOLOPYRIDAZINE-SULFANYL) BENZOTHIAZOLES AND BENZIMIDAZOLES, PREPARATION THEREOF, USE THEREOF AS DRUGS, AND USE THEREOF AS MET INHIBITORS

The present invention relates to novel 6-O-cycloalkyl- or 6-NH-cycloalkyl-triazolopyridazine-sulfanyl benzothiazole and benzimidazole derivatives, to a process for preparing them, to the novel intermediates obtained, to their use as medicaments, to pharmaceutical compositions containing them and to the novel use of such 6-triazolopyridazine-sulfanyl benzothiazole and benzimidazole derivatives.

The present invention more particularly relates to novel 6-O-cycloalkyl or 6-NH-cycloalkyl-triazolopyridazine-sulfanyl benzothiazole and benzimidazole derivatives with anticancer activity, via modulation of the activity of proteins, in particular kinases.

To date, most of the commercial compounds used in chemotherapy are cytotoxic and pose major problems of side effects and tolerance by patients. These effects can be limited if the medicaments used act selectively on cancer cells, to the exclusion of healthy cells. One of the solutions for limiting the undesirable effects of a chemotherapy may thus consist in using medicaments that act on metabolic pathways or constituent elements of these pathways, predominantly expressed in cancer cells, and not expressed or only sparingly expressed in healthy cells. Kinase proteins are a family of enzymes that catalyse the phosphorylation of hydroxyl groups of specific protein residues such as tyrosine, serine or threonine residues. Such phosphorylations may widely modify the function of proteins: thus, kinase proteins play an important role in regulating a wide variety of cellular processes, especially including cell metabolism and proliferation, cellular

adhesion and motility, cell differentiation or cell survival, certain kinase proteins playing a central role in the initiation, development and completion of cell cycle events.

Among the various cellular functions in which the activity of a kinase protein is involved, certain processes represent attractive targets for treating certain diseases. Examples that may especially be mentioned include angiogenesis and control of the cell cycle and also that of cell proliferation, in which kinase proteins may play an essential role. These processes are especially essential for the growth of solid tumours and also other diseases: in particular, molecules that inhibit such kinases are capable of limiting undesired cell proliferations such as those observed in cancers, and can intervene in the prevention, regulation or treatment of neurodegenerative diseases such as Alzheimer's disease or neuronal apoptosis.

One subject of the present invention is novel derivatives endowed with inhibitory effects on kinase proteins. The products according to the present invention may thus be used especially for preventing or treating diseases that can be modulated by inhibiting kinase proteins.

The products according to the present invention especially show anticancer activity, via modulation of the activity of kinases. Among the kinases for which activity modulation is desired, MET and also mutants of the protein MET are preferred.

The present invention also relates to the use of the said derivatives for preparing a medicament for treating man.

Thus, one of the objects of the present invention is to propose compositions with anticancer activity, by acting in particular on kinases. Among the kinases for which activity modulation is desired, MET is preferred.

In the pharmacological section hereinbelow, it is shown in biochemical tests and on cell lines that the products of the present patent application thus especially inhibit the autophosphorylation activity of MET and the proliferation of cells whose growth is dependent on MET or mutants forms thereof.

MET, or Hepatocyte Growth Factor Receptor, is a receptor with tyrosine kinase activity that is expressed in particular in epithelial and endothelial cells. HGF, Hepatocyte Growth Factor, is described as the specific ligand of MET. HGF is secreted by mesenchymal cells and activates the MET receptor, which homodimerizes. Consequently, the receptor becomes autophosphorylated on tyrosines Y1230, Y1234 and Y1235 of the catalytic domain.

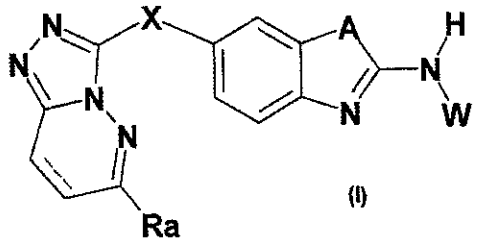
Stimulation of MET with HGF induces cell proliferation, scattering (or dispersion) and motility, resistance to apoptosis, invasion and angiogenesis.

MET and likewise HGF are found to be overexpressed in many human tumours and a wide variety of cancers. MET is also found to be amplified in gastric tumours and glioblastomas. Many point mutations of the MET gene have also been described in tumours, in particular in the kinase domain, but also in the juxtamembrane domain and the SEMA domain. Overexpression, amplification or mutations cause constitutive activation of the receptor and deregulation of its functions.

The present invention thus relates especially to novel inhibitors of the kinase protein MET and mutants thereof, which may be used for anti-proliferative and anti-metastatic treatment especially in oncology.

The present invention also relates to novel inhibitors of the kinase protein MET and mutants thereof, which may be used for anti-angiogenic treatment, especially in oncology.

One subject of the present invention is the products of formula (I):



(I)

in which

---- represents a single or double bond;

Ra represents a radical -O-cycloalkyl, or a radical -NH-cycloalkyl, both optionally substituted;

X represents S, SO or SO2;

A represents NH or S;

W represents a hydrogen atom; an alkyl radical optionally substituted with alkoxy, heterocycloalkyl or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical, optionally substituted with a halogen atom or a radical cycloalkyl, NR3R4, alkoxy, hydroxyl, phenyl, heteroaryl or heterocycloalkyl, which are themselves optionally substituted;
- an alkoxy radical optionally substituted with NR3R4, alkoxy, hydroxyl or heterocycloalkyl; a radical O-phenyl or a radical O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 4;
- or the radical NR1R2 in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical and the other from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical, a heterocycloalkyl radical or an alkyl radical optionally substituted with one or more radicals, which

may be identical or different, chosen from the following radicals: hydroxyl, alkoxy, heteroaryl, heterocycloalkyl, NR3R4, phenyl, optionally substituted or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, with the optional S possibly being in the form SO or SO2; this radical, including the possible NH it contains, being optionally substituted;

with R3 and R4, which may be identical or different, representing a hydrogen atom, an alkyl radical, a cycloalkyl radical, a heterocycloalkyl radical, a heteroaryl radical or a phenyl radical, all optionally substituted with one or more radicals, which may be identical or different, chosen from the following radicals: hydroxyl, alkoxy, heteroaryl, heterocycloalkyl, NH2, NHAlk, N(Alk)2 or phenyl optionally substituted; or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, with the optional S possibly being in the form SO or SO2; this radical, including the possible NH it contains, being optionally substituted;

all the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl and phenyl radicals defined above, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, being optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkoxy, -O-CO-R5, -COOH, COOR5, -CONH2, CONHR5, NH2, NHR5, NR5R5', -NH-CO-R5 and alkyl, cycloalkyl, heterocycloalkyl, CH2-heterocycloalkyl, phenyl, CH2-phenyl, CO-phenyl, heteroaryl and S-heteroaryl radicals, such that in the latter radicals, the alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl radicals are themselves optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkyl and alkoxy containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2,

all the cycloalkyl, heterocycloalkyl, heteroaryl and phenyl radicals defined above being furthermore optionally substituted with a radical Si(alk)3;
it being possible for all the cycloalkyl and heterocycloalkyl radicals defined above to be optionally substituted on one of the carbons of the ring by a spirocycloalkyl or spiroheterocycloalkyl radical or optionally on two of the carbons of the ring by a fused cycloalkyl or heterocycloalkyl radical;
R5 and R5', which may be identical or different, represent an alkyl or cycloalkyl radical containing not more than 6 carbon atoms;
alk represents an alkyl radical containing not more than 4 carbon atoms;
it being understood that W does not represent H when A represents S, X represents S, Ra represents the unsubstituted O-cyclohexyl radical or the unsubstituted NH-cyclohexyl radical and ---- represents a double bond,
the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which

---- represents a single or double bond;
Ra represents a radical -O-cycloalkyl or a radical -NH-cycloalkyl optionally substituted;
X represents S, SO or SO_2;
A represents NH or S;
W represents a hydrogen atom, an alkyl radical optionally substituted with alkoxy, heterocycloalkyl or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical, optionally substituted with a halogen atom or a radical cycloalkyl, NR3R4, alkoxy, hydroxyl, phenyl, heteroaryl or heterocycloalkyl, which are themselves optionally substituted;

- an alkoxy radical optionally substituted with NR3R4, alkoxy, hydroxyl or heterocycloalkyl; a radical O-phenyl or a radical O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 4;
- or the radical NR1R2 in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical and the other from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical, a heterocycloalkyl radical or an alkyl radical optionally substituted with one or more radicals, which may be identical or different, chosen from the following radicals: hydroxyl, alkoxy, heteroaryl, heterocycloalkyl, NR3R4, phenyl, optionally substituted or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, with the optional S possibly being in the form SO or SO2, this radical, including the possible NH it contains, being optionally substituted;

with R3 and R4, which may be identical or different, representing a hydrogen atom, an alkyl radical, a cycloalkyl radical, a heterocycloalkyl radical, a heteroaryl radical or a phenyl radical, all optionally substituted with one or more radicals, which may be identical or different, chosen from the following radicals: hydroxyl, alkoxy, heteroaryl, heterocycloalkyl, NH2, NHAlk, N(Alk)2 or phenyl, optionally substituted; or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, with the optional S possibly being in the form SO or SO2, this radical, including the possible NH it contains, being optionally substituted;

all the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl and phenyl radicals defined above, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, being optionally substituted with one or more radicals chosen

from halogen atoms and the following radicals: hydroxyl, oxo, alkoxy, -O-CO-R5, NH2, NHalk, N(alk)2 and alkyl, cycloalkyl, heterocycloalkyl, CH2-heterocycloalkyl, phenyl, CH2-phenyl, CO-phenyl, heteroaryl and S-heteroaryl radicals, such that in the latter radicals, the alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl radicals are themselves optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkyl and alkoxy containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2;

R5 represents an alkyl or cycloalkyl radical containing not more than 6 carbon atoms;

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which ----- , Ra and X have the values defined in any one of the other claims, and:

A represents NH or S;

W represents a hydrogen atom; an alkyl radical optionally substituted with alkoxy, heterocycloalkyl or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical optionally substituted with a halogen atom or a radical cycloalkyl, NR3R4, alkoxy, hydroxyl, phenyl or heterocycloalkyl, which are themselves optionally substituted;
- an alkoxy radical optionally substituted with NR3R4, alkoxy, hydroxyl or heterocycloalkyl; a radical O-phenyl or a radical O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 4;
- or the radical NR1R2, in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom or an alkyl radical and the other from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical, a heterocycloalkyl radical or an alkyl radical

optionally substituted with an alkoxy or heterocycloalkyl radical, or NR3R4; or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

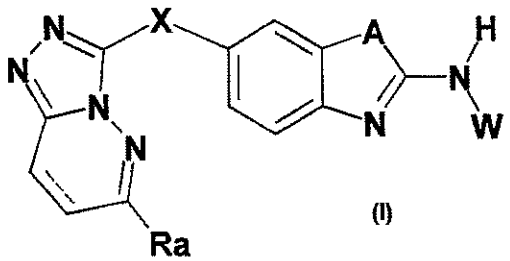
- with NR3R4 such that R3 and R4, which may be identical or different, represent a hydrogen atom or an alkyl radical or a heterocycloalkyl radical, all optionally substituted with one or more radicals, which may be identical or different, chosen from alkoxy or heterocycloalkyl radicals or NH2, NHAlk or N(Alk)2; or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

all the cycloalkyl, heterocycloalkyl and phenyl radicals, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, defined above, being optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, alkoxy, NH2, NHalk, N(alk)2 and alkyl, heterocycloalkyl, CH2-heterocycloalkyl, phenyl, CH2-phenyl and heteroaryl radicals, such that in the latter radicals, the alkyl, heterocycloalkyl, phenyl and heteroaryl radicals are themselves optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, alkyl and alkoxy radicals containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2;

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

As regards the cyclic radicals that can be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, these radicals optionally containing one or more other heteroatoms chosen from O, S, N and NH, with the optional S possibly being in the form SO or SO2; these radicals, including the optional NH they contain, may thus be optionally substituted especially with a radical chosen from alkyl, alkoxy, cycloalkyl and heterocycloalkyl, which are themselves optionally substituted with one or more radicals chosen from halogen atoms and the radicals alkyl, alkoxy, NH2, NHAlk and N(Alk)2;

One subject of the present invention is the products of formula (I):



(I)

in which

---- represents a single or double bond;

Ra represents a radical -O-cycloalkyl, or a radical -NH-cycloalkyl, both optionally substituted;

X represents S, SO or SO2;

A represents NH or S;

W represents a hydrogen atom; an alkyl radical optionally substituted with alkoxy, heterocycloalkyl or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical, optionally substituted with a radical NR3R4, alkoxy, hydroxyl, phenyl, heteroaryl or heterocycloalkyl, which are themselves optionally substituted;
- an alkoxy radical optionally substituted with NR3R4, alkoxy, hydroxyl or heterocycloalkyl; a radical O-phenyl or a radical O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 4;

- or the radical NR1R2 in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical and the other from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical optionally substituted with one or more radicals, which may be identical or different, chosen from the following radicals: hydroxyl, alkoxy, heteroaryl, heterocycloalkyl, NR3R4, phenyl, optionally substituted or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

with R3 and R4, which may be identical or different, representing a hydrogen atom, an alkyl radical, a cycloalkyl radical, a heteroaryl radical or a phenyl radical, all optionally substituted, or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

all the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl and phenyl radicals defined above, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, being optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkoxy, -O-CO-R5, -COOH, COOR5, -CONH2, CONHR5, NH2, NHR5, NR5R5', -NH-CO-R5 and alkyl, cycloalkyl, CH2-heterocycloalkyl, phenyl, CH2-phenyl, CO-phenyl, heteroaryl and S-heteroaryl radicals, such that in the latter radicals, the alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl radicals are themselves optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkyl and alkoxy containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2,

all the cycloalkyl, heterocycloalkyl, heteroaryl and phenyl radicals defined above being furthermore optionally substituted with a radical Si(alk)3;
R5 and R5', which may be identical or different, represent an alkyl or cycloalkyl radical containing not more than 6 carbon atoms;
alk represents an alkyl radical containing not more than 4 carbon atoms;
it being understood that W does not represent H when A represents S, X represents S, Ra represents the unsubstituted O-cyclohexyl radical or the unsubstituted NH-cyclohexyl radical and ---- represents a double bond,
the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which

---- represents a single or double bond;
Ra represents a radical -O-cycloalkyl or a radical -NH-cycloalkyl both optionally substituted;
X represents S, SO or SO_2;
A represents NH or S;
W represents a hydrogen atom, an alkyl radical optionally substituted with alkoxy, heterocycloalkyl or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical, optionally substituted with a radical NR3R4, alkoxy, hydroxyl, phenyl, heteroaryl or heterocycloalkyl, which are themselves optionally substituted;
- an alkoxy radical optionally substituted with NR3R4, alkoxy, hydroxyl or heterocycloalkyl; a radical O-phenyl or a radical O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 4;

- or the radical NR1R2 in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical and the other from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical optionally substituted with one or more radicals, which may be identical or different, chosen from the following radicals: hydroxyl, alkoxy, heteroaryl, heterocycloalkyl, NR3R4, phenyl, optionally substituted or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

with R3 and R4, which may be identical or different, representing a hydrogen atom, an alkyl radical, a cycloalkyl radical, a heteroaryl radical or a phenyl radical, which is optionally substituted, or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

all the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl and phenyl radicals defined above, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, being optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkoxy, -O-CO-R5, NH2, NHalk, N(alk)2 and alkyl, cycloalkyl, heterocycloalkyl, CH2-heterocycloalkyl, phenyl, CH2-phenyl, CO-phenyl, heteroaryl and S-heteroaryl radicals, such that in the latter radicals, the alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl radicals are themselves optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkyl and alkoxy containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2;

R5 represents an alkyl or cycloalkyl radical containing not more than 6 carbon atoms;

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which ---- , Ra and X have the values defined in any one of the other claims, and:

A represents NH or S;

W represents a hydrogen atom; an alkyl radical optionally substituted with alkoxy, heterocycloalkyl or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical optionally substituted with a radical NR3R4, alkoxy, hydroxyl, phenyl or heterocycloalkyl, which are themselves optionally substituted;
- an alkoxy radical optionally substituted with NR3R4, alkoxy, hydroxyl or heterocycloalkyl; a radical O-phenyl or a radical O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 4;
- or the radical NR1R2, in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom or an alkyl radical and the other from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical optionally substituted with an alkoxy or heterocycloalkyl radical, or NR3R4; or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

with NR3R4 such that R3 and R4, which may be identical or different, represent a hydrogen atom or an alkyl radical or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic

radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

all the cycloalkyl, heterocycloalkyl and phenyl radicals, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, defined above, being optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, alkoxy, NH2, NHalk, N(alk)2 and alkyl, heterocycloalkyl, CH2-heterocycloalkyl, phenyl, CH2-phenyl and heteroaryl radicals, such that in the latter radicals, the alkyl, heterocycloalkyl, phenyl and heteroaryl radicals are themselves optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, alkyl and alkoxy radicals containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2;

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which ---- , Ra and X have the values defined in any one of the other claims, and:

A represents NH or S;

W represents a hydrogen atom; an alkyl radical optionally substituted with a heterocycloalkyl radical or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical optionally substituted with a radical NR3R4, or alkoxy;
- a radical O-phenyl or O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 2;
- or the radical NR1R2, in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical and the other from among R1 and R2 represents a hydrogen

atom, an alkyl radical optionally substituted with a heterocyclic radical or NR3R4, or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

with NR3R4 such that R3 and R4, which may be identical or different, represent a hydrogen atom or an alkyl radical or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

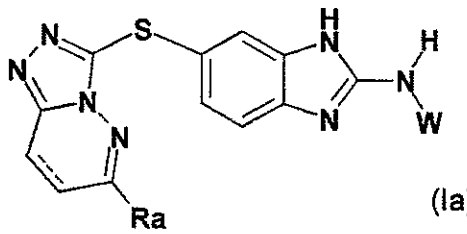
all the cycloalkyl, heterocyclic and phenyl radicals, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, defined above, being optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, alkoxy, NH2, NHalk, N(alk)2 and alkyl and phenyl radicals, the latter radicals themselves being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, alkyl and alkoxy radicals containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2;

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

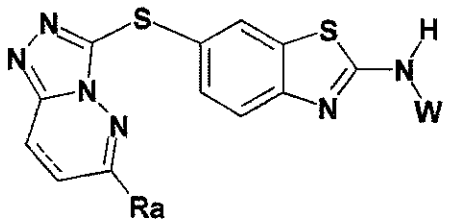
A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which A represents NH, the substituents  , Ra, X and W being chosen from all the values defined for these radicals in any one of the other claims, the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which A represents S, the substituents ---- , Ra, X and W being chosen from all the values defined for these radicals in any one of the other claims, the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

One subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow corresponding to formula (Ia) or (Ib):



(Ia)

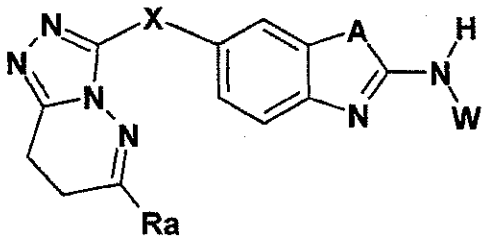


(Ib)

in which ---- , Ra and W are chosen from the meanings indicated in any one of the other claims,

the said products of formula (Ia) and (Ib) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formulae (Ia) and (Ib).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which ---- represents a single bond, corresponding to the products of formula (I'):

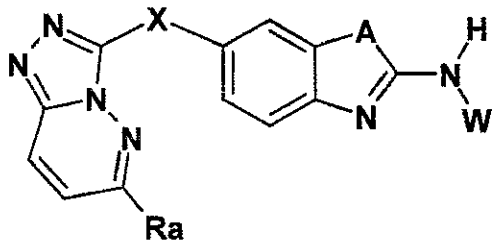


(I')

the substituents Ra, X, A and W having the meanings indicated in any one of the other claims,

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which ---- represents a double bond, corresponding to the products of formula (I''):

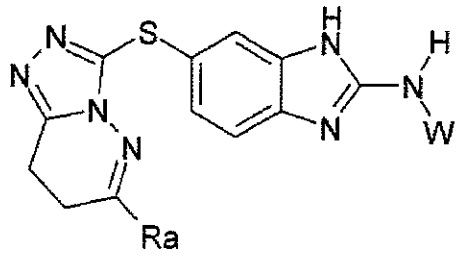


(I'')

in which the substituents Ra, X, A and W have the meanings indicated in any one of the other claims,

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which ---- represents a single bond, corresponding to the products of formula (Ia'):

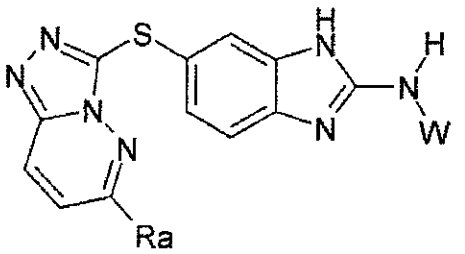


(I'a)

in which Ra and W are chosen from the meanings indicated in any one of the other claims,

the said products of formula (I'a) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I'a).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which ---- represents a double bond, corresponding to the products of formula (I''a):

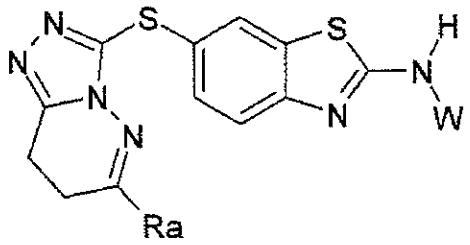


(I''a)

in which Ra and W are chosen from the meanings indicated in any one of the other claims,

the said products of formula (I''a) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I''a).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which ---- represents a single bond, corresponding to the products of formula (I'b):

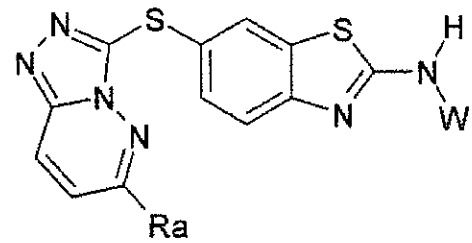


(I'b)

in which Ra and W are chosen from the meanings indicated in any one of the other claims,

the said products of formula (I'b) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I'b).

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which ---- represents a double bond, corresponding to the products of formula (I''b):



(I''b)

in which Ra and W are chosen from the meanings indicated in any one of the other claims,

the said products of formula (I''b) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I''b).

In the products of formula (I) and in the text hereinbelow:

- the term alkyl radical (or Alk) denotes linear and, where appropriate, branched methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, isohexyl and also heptyl, octyl, nonyl and decyl

radicals, and also the linear or branched positional isomers thereof: alkyl radicals containing from 1 to 6 carbon atoms and more particularly alkyl radicals containing from 1 to 4 carbon atoms of the above list are preferred;

- the term alkoxy radical denotes linear and, where appropriate, branched methoxy, ethoxy, propoxy or isopropoxy, secondary or tertiary linear butoxy, pentoxy or hexoxy, and also the linear or branched positional isomers thereof: alkoxy radicals containing from 1 to 4 carbon atoms of the above list are preferred;

- the term halogen atom denotes a chlorine, bromine, iodine or fluorine atom and preferably the chlorine, bromine or fluorine atom.

- the term cycloalkyl radical denotes a saturated carbocyclic radical containing 3 to 10 carbon atoms and thus especially denotes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl radicals and most particularly cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl radicals;

- the term heterocycloalkyl radical thus denotes a 3- to 10-membered monocyclic or bicyclic carbocyclic radical interrupted with one or more heteroatoms, which may be identical or different, chosen from oxygen, nitrogen and sulfur atoms: examples that may be mentioned include morpholinyl, thiomorpholinyl, aziridyl, azetidyl, piperazinyl, piperidyl, homopiperazinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, tetrahydrofuryl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl and oxodihydropyridazinyl radicals, or alternatively oxetanyl or thietanyl radicals, all these radicals being optionally substituted; it may be noted that these heterocycloalkyl radicals may comprise a bridge formed from two ring members to form, for example, an oxa-5-azabicyclo[2.2.1]heptane or an azaspiro[3.3]heptane radical or other azabicycloalkane or azaspiroalkane rings.

- the terms aryl and heteroaryl denote unsaturated or partially unsaturated monocyclic or bicyclic, carbocyclic and heterocyclic radicals, respectively, which are not more than 12-membered, possibly containing a -C(O) ring member, the heterocyclic radicals containing one or more heteroatoms, which

may be identical or different, chosen from O, N and S with N, where appropriate, being optionally substituted;

- the term aryl radical thus denotes 6- to 12-membered monocyclic or bicyclic radicals, for instance phenyl, naphthyl, biphenyl, indenyl, fluorenyl and anthracenyl radicals, more particularly phenyl and naphthyl radicals and even more particularly the phenyl radical. It may be noted that a carbocyclic radical containing a -C(O) ring member is, for example, the tetralone radical;

- the term heteroaryl radical thus denotes 5- to 12-membered monocyclic or bicyclic radicals: monocyclic heteroaryl radicals, for instance thienyl radicals such as 2-thienyl and 3-thienyl, furyl such as 2-furyl, 3-furyl, pyranyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, pyridyl such as 2-pyridyl, 3-pyridyl and 4-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, isothiazolyl, diazolyl, thiadiazolyl, thiatriazolyl, oxadiazolyl, isoxazolyl such as 3- or 4-isoxazolyl, furazanyl, free or salified tetrazolyl, all these radicals being optionally substituted, among which more particularly are thienyl radicals such as 2-thienyl and 3-thienyl, furyl such as 2-furyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridyl and pyridazinyl, these radicals being optionally substituted; bicyclic heteroaryl radicals, for instance benzothienyl radicals such as 3-benzothienyl, benzothiazolyl, quinolyl, isoquinolyl, dihydroquinolyl, quinolone, tetralone, adamantyl, benzofuryl, isobenzofuryl, dihydrobenzofuryl, ethylenedioxyphenyl, thianthrenyl, benzopyrrolyl, benzimidazolyl, benzoxazolyl, thionaphthyl, indolyl, azaindolyl, indazolyl, purinyl, thienopyrazolyl, tetrahydroindazolyl, tetrahydrocyclopentapyrazolyl, dihydrofuropyrazolyl, tetrahydropyrrolopyrazolyl, oxotetrahydropyrrolopyrazolyl, tetrahydropyranopyrazolyl, tetrahydropyridinopyrazolyl or oxodihydropyridinopyrazolyl, all these radicals being optionally substituted.

As examples of heteroaryl or bicyclic radicals, mention may be made more particularly of pyrimidinyl, pyridyl, pyrrolyl, azaindolyl, indazolyl or pyrazolyl

radicals, optionally substituted with one or more identical or different substituents as indicated above.

The carboxyl radical(s) of the products of formula (I) may be salified or esterified with various groups known to those skilled in the art, among which examples that may be mentioned include:

- among the salification compounds, mineral bases such as, for example, one equivalent of sodium, potassium, lithium, calcium, magnesium or ammonium, or organic bases, for instance methylamine, propylamine, trimethylamine, diethylamine, triethylamine, N,N-dimethylethanolamine, tris(hydroxymethyl)-aminomethane, ethanolamine, pyridine, picoline, dicyclohexylamine, morpholine, benzylamine, procaine, lysine, arginine, histidine or N-methyl-glucamine,
- among the esterification compounds, alkyl radicals to form alkoxycarbonyl groups, for instance methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl or benzyloxycarbonyl, these alkyl radicals possibly being substituted with radicals chosen, for example, from halogen atoms and hydroxyl, alkoxy, acyl, acyloxy, alkylthio, amino and aryl radicals, for instance in chloromethyl, hydroxypropyl, methoxymethyl, propionyloxymethyl, methylthiomethyl, dimethylaminoethyl, benzyl or phenethyl groups.

The addition salts with mineral or organic acids of the products of formula (I) may be, for example, the salts formed with hydrochloric, hydrobromic, hydriodic, nitric, sulfuric, phosphoric, propionic, acetic, trifluoroacetic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic or ascorbic acid, alkylmonosulfonic acids, for instance methanesulfonic acid, ethanesulfonic acid, propanesulfonic acid, alkyldisulfonic acids, for instance methanedisulfonic acid, α,β-ethanedisulfonic acid, arylmonosulfonic acids such as benzenesulfonic acid, and aryldisulfonic acids.

It may be recalled that stereoisomerism may be defined in its broadest sense as isomerism of compounds having the same structural formulae, but whose various groups are arranged differently in space, especially such as in monosubstituted cyclohexanes in which the substituent may be in an axial or equatorial position, and the various possible rotational conformations of ethane derivatives. However, another type of stereoisomerism exists, due to the various spatial arrangements of fixed substituents, either on double bonds, or on rings, which is often referred to as geometrical isomerism or cis-trans isomerism. The term stereoisomers is used in the present patent application in its broadest sense and thus concerns all the compounds indicated above.

The cyclic radicals that may be formed, on the one hand, by R1 and R2 with the nitrogen atom to which they are attached, and, on the other hand, by R3 and R4 with the nitrogen atom to which they are attached, are optionally substituted with one or more radicals chosen from those indicated above for the possible substituents on the heterocycloalkyl radicals, i.e. one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkoxy, NH2; NHalk, N(alk)2, and alkyl, heterocycloalkyl, CH2-heterocycloalkyl, phenyl, CH2-phenyl, heteroaryl and CO-phenyl radicals, such that in the latter radicals the alkyl, heterocycloalkyl and phenyl radicals are themselves optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkyl and alkoxy containing from 1 to 4 carbon atoms, NH2; NHalk and N(alk)2.

The cyclic radicals that may be formed, on the one hand, by R1 and R2 with the nitrogen atom to which they attached, and, on the other hand, by R3 and R4 with the nitrogen atom to which they are attached, are especially optionally substituted with one or more identical or different radicals chosen from halogen atoms and alkyl, hydroxyl, alkoxy, CH2-pyrrolidinyl, CH2-phenyl, heteroaryl and phenyl radicals, in which the alkyl, pyrrolidinyl and

phenyl radicals are themselves optionally substituted with one or more identical or different radicals chosen from halogen atoms and alkyl, hydroxyl, oxo and alkoxy radicals.

The heterocycloalkyl radicals as defined above especially represent azepanyl, morpholinyl, pyrrolidinyl, piperidyl and piperazinyl radicals, which are themselves optionally substituted, as defined hereinabove or hereinbelow.

When NR1R2 or NR3R4 forms a ring as defined above, such an amine ring may be chosen especially from pyrrolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, azepinyl, morpholinyl and piperazinyl radicals, these radicals themselves being optionally substituted as indicated hereinabove or hereinbelow: for example with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl, hydroxyl, alkoxy, phenyl and CH2-phenyl radicals, the alkyl or phenyl radicals themselves being optionally substituted with one or more identical or different radicals chosen from halogen atoms and alkyl, hydroxyl and alkoxy radicals.

The ring NR1R2 or NR3R4 may be chosen more particularly from pyrrolidinyl and morpholinyl radicals optionally substituted with one or two alkyl or piperazinyl radicals optionally substituted on the second nitrogen atom with an alkyl, phenyl or CH2-phenyl radical, which are themselves optionally substituted with one or more identical or different radicals chosen from halogen atoms and alkyl, hydroxyl and alkoxy radicals.

A subject of the present invention is the products of formula (I) as defined hereinabove or hereinbelow, in which

---- represents a single or double bond

Ra represents a radical -O-cycloalkyl, or a radical -NH-cycloalkyl optionally substituted with a hydroxyl, alkoxy or -O-CO-R5 radical;

X represents S;

A represents S;

W represents a hydrogen atom or an alkyl radical optionally substituted with heterocycloalkyl or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical, optionally substituted with a radical NR3R4, or alkoxy;
- a radical O-phenyl;
- or the radical NR1R2 in which R1 and R2 are such that one represents a hydrogen atom and the other represents an alkyl radical optionally substituted with a heterocycloalkyl radical;

with NR3R4 such that R3 and R4, which may be identical or different, represent a hydrogen atom or an alkyl radical;

R5 represents an alkyl or cycloalkyl radical containing at most 6 carbon atoms;

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

Especially in the products of formula (I), the cycloalkyl radicals can represent a cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl or cyclopropyl radical;

Especially in the products of formula (I), the heterocycloalkyl radicals can represent a morpholinyl or pyrrolidinyl radical.

A subject of the present invention is thus the products of formula (I) as defined hereinabove or hereinbelow, corresponding to the following formulae:

- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea

- 1-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- 1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea
- N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- N-[6-({6-[(trans-4-hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- 1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea
- 6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-N-[2-(pyrrolidin-1-yl)ethyl]-1,3-benzothiazol-2-amine
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-methoxyacetamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2,N^2-dimethylglycinamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methylbutanamide

- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide
- 6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine
- N-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- N-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- 6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine
- N-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- trans-4-{[3-({2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}sulfanyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]amino}cyclohexyl cyclopropanecarboxylate
- N-[6-({6-[(trans-4-hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]acetamide
- 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclopropyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2,N^2-dimethylglycinamide
- 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclohexyl-7,8-dihydro[1,2,4]-triazolo[4,3-b]pyridazin-6-amine
- ethyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate
- 2-chloro-N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide

- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²-cyclopropylglycinamide
- 6-[(6-{[4-(trifluoromethyl)cyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-amine
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²,N²-diethylglycinamide
- N-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- 1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[3-(morpholin-4-yl)propyl]urea
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[3-(morpholin-4-yl)propyl]urea
- 1-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-[2-(morpholin-4-yl)ethyl]-3-{6-[(6-{[4-(trifluoromethyl)cyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-cyclopropylacetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- rac-cis/trans-N-{4-[(3-{[2-({[2-(morpholin-4-yl)ethyl]carbamoyl}amino)-1,3-benzothiazol-6-yl]sulfanyl}[1,2,4]triazolo[4,3-b]pyridazin-6-yl)oxy]cyclohexyl}-acetamide
- N-{6-[(6-{[4-(trifluoromethyl)cyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- 1-[6-({6-[(trans-4-hydroxycyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}-sulfanyl)-1,3-benzothiazol-2-yl]-3-[2-(morpholin-4-yl)ethyl]urea
- 6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine

- 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclobutyl[1,2,4]triazolo[4,3-b]-pyridazin-6-amine
- N-(6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)cyclobutanecarboxamide
- rac-6-({6-[(trans-2-fluorocyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}-sulfanyl)-1,3-benzothiazol-2-amine
- rac-N-{6-[(6-{[(trans-2-fluorocyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- N-(6-{[6-(cyclobutylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- N-(6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- rac-N^2,N^2-diethyl-N-[6-({6-[(trans-2-fluorocyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]glycinamide
- rac-2-(4-ethylpiperazin-1-yl)-N-{6-[(6-{[trans-2-fluorocyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}acetamide
- rac-N-{6-[(6-{[trans-2-fluorocyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-2-(morpholin-4-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(morpholin-4-yl)acetamide
- rac-2-(4-cyclopropylpiperazin-1-yl)-N-{6-[(6-{[trans-2-fluorocyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(4-cyclopropylpiperazin-1-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(1,1-dioxidothiomorpholin-4-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(1,4-oxazepan-4-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide

- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(3,3-difluoropiperidin-1-yl)acetamide
- rac-cis/trans-1-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea
- rac-cis/trans-N-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- rac-cis/trans-1-[6-({6-[(4-methylcyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(piperidin-1-yl)azetidine-1-carboxamide
- rac-cis/trans-N-[6-({6-[(4-methylcyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(morpholin-4-yl)azetidine-1-carboxamide
- rac-N-{6-[(6-{[trans-2-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- rac-1-{6-[(6-{[trans-2-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxyazetidine-1-carboxamide
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-oxetan-3-ylurea
- rac-cis/trans-1-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea
- rac-cis/trans-N-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide

and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is also any process for preparing the products of formula (I) as defined above.

A subject of the present invention is thus any process for preparing the products of formula (I) as defined above, in which A represents NH.

A subject of the present invention is thus any process for preparing the products of formula (I) as defined above, in which A represents S.

The products according to the invention may be prepared from conventional methods of organic chemistry. Schemes 1, 2, 3, 4, 5 and 6 hereinbelow illustrate methods used for the preparation of the products of formula (I). In this respect, they shall not constitute a limitation of the scope of the invention, as regards the methods for preparing the claimed compounds.

The products of formula (I) as defined above according to the present invention may thus especially be prepared according to the processes described in Schemes 1, 2, 2bis, 3, 4, 5 and 6 hereinbelow.

A subject of the present invention is thus also the process for preparing products of formula (I) according to Scheme 1 as defined below.

A subject of the present invention is thus also the process for preparing products of formula (I) according to Scheme 2 as defined below.

A subject of the present invention is thus also the process for preparing products of formula (I) according to Scheme 2bis as defined below.

A subject of the present invention is thus also the process for preparing products of formula (I) according to Scheme 3 as defined below.

A subject of the present invention is thus also the process for preparing products of formula (I) according to Scheme 4 as defined below.

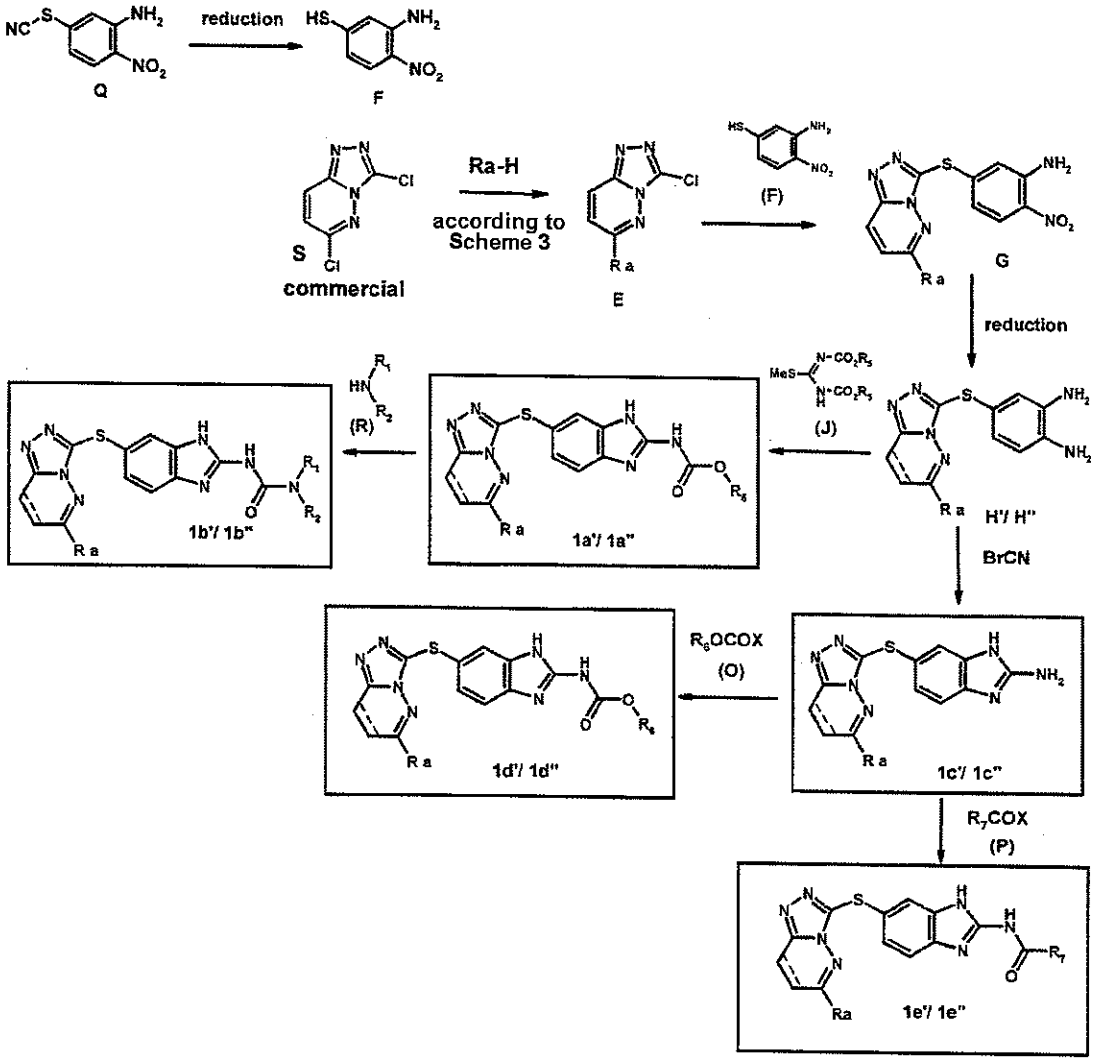
A subject of the present invention is thus also the process for preparing products of formula (I) according to Scheme 5 as defined below.

A subject of the present invention is thus also the process for preparing products of formula (I) according to Scheme 6 as defined below.

Similarly, among the products of formula (I) as defined above in which ---- represents a single or double bond, the products of formula (I') are defined, which represent products of formula (I) in which ---- represents a single bond and products of formula (I'') which represent products of formula (I) in which ---- represents a double bond,

and similarly, for the synthetic intermediates as defined below of formulae (a), (b), (c), (d), (e) and (f) in which ---- represents a single or double bond, the compounds of formulae (a'), (b'), (c'), (d'), (e') and (f') are defined, in which ---- represents a single bond, and the compounds of formulae (a''), (b''), (c''), (d''), (e'') and (f'') in which ---- represents a double bond.

Scheme 1: synthesis of benzimidazole derivatives of formulae (1a''), (1b''), (1''c), (1d''), (1e''), (1a'), (1b'), (1c'), (1d') and (1e')

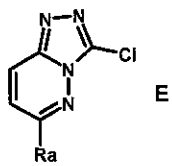


In Scheme 1 above, the substituent Ra may take the meanings given above for the products of formulae (I') and (I''), substituent R5, in the compounds of formulae (J), (1a') and (1a''), represents an alkyl radical and the substituent R6, in the compounds of formulae (O), (1d') and (1d''), represents an alkyl radical optionally substituted with NR3R4 (a -(CH2)n-NR3R4 radical), alkoxy, hydroxyl, heterocycloalkyl, phenyl or -(CH2)n-phenyl, with phenyl being optionally substituted and n representing an integer from 1 to 4. The substituent R7 in the compounds of formulae (P) and (1e')/(1e'') represents a cycloalkyl or alkyl radical optionally substituted with an NR3R4, alkoxy,

hydroxyl, phenyl, heteroaryl or heterocycloalkyl radical, themselves optionally substituted.

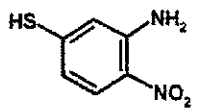
In Scheme 1 above, the groups CONR1R2, CO2R6 and COR7, which constitute W, may take the values of W as defined above for the products of formulae (I') and (I''), when W≠H

In the above Scheme 1, the benzimidazoles of general formulae (1a''), (1b''), (1c''), (1d'') and (1e'') and also the reduced analogues thereof of general formulae (1a'), (1b'), (1c'), (1d') and (1e') may be prepared from commercial 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine of formula (S).

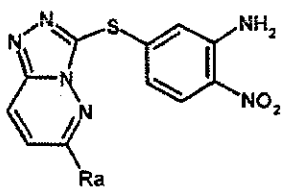


E

The compounds (E) may be obtained, for example, by reaction of alcohols or amines in the presence or absence of a base on the compound (S). The reaction is performed, for example, at a temperature in the region of 20°C to 80°C.



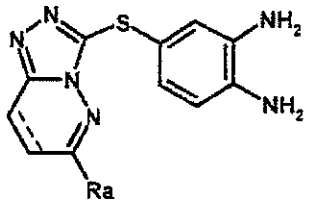
F



G

The compounds (G) may be obtained, for example, by reacting 3-amino-4-nitrobenzenethiol of formula (F) with the compounds of formula (E). The compounds of formula (F) are obtained via *in situ* reduction of 3-amino-4-nitrophenyl thiocyanate (Q) (commercial compound), for example, in the

presence of sodium borohydride in a solvent such as N,N-dimethylformamide, at a temperature in the region of 20°C.



H'/H"

The compounds (H") such that ---- represent a double bond may be obtained, for example, via reduction with iron (0) on the compounds of formula (G), in a solvent such as methanol, in the presence of acetic acid, at a temperature in the region of 70°C.

The compounds (H') such that ---- represent a single bond may be obtained, for example, via reduction with zinc (0) of the compounds of formula (G), in the presence of acetic acid, at a temperature in the region of 20°C.

More particularly, the carbamates of general formulae (1a') and (1a") may especially be prepared as described in patent WO 03/028721 A2, starting, respectively, with a 3,4-diaminophenyl sulfide of formulae (H') and (H") and with a pseudo thiourea of formula (J), in the presence of acetic acid and in a protic solvent such as methanol, at a temperature in the region of 80°C.

More particularly, the benzimidazoles of general formulae (1b') and (1b") may be prepared, respectively, by reaction of an amine NHR1R2 of formula (R) (with R1 and R2 as defined above) with a carbamate of formulae (1a') and (1a"), for example in the presence of an aprotic solvent such as 1-methyl-2-pyrrolidinone. The reaction is performed, for example, at a temperature in the region of 120°C, in a sealed tube under microwaves.

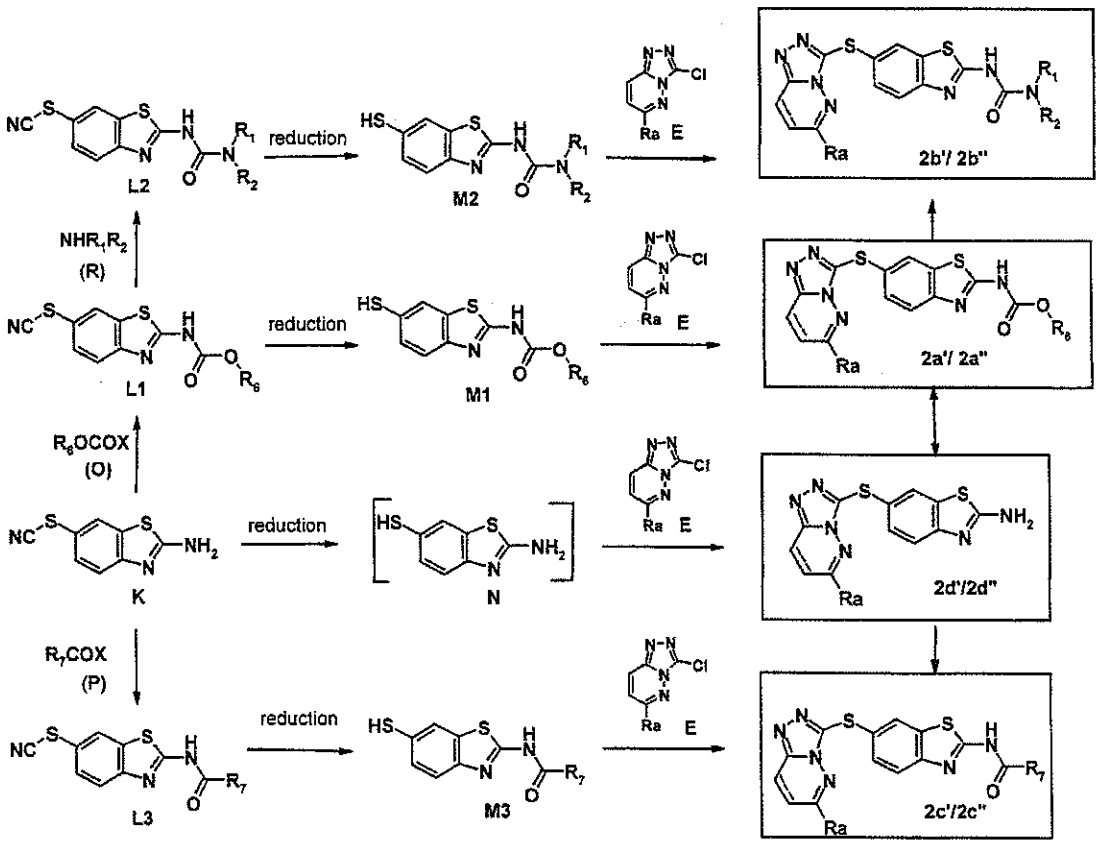
More particularly, the 2-aminobenzimidazoles of general formulae (1c') and (1c") may be prepared, for example, by reacting cyanogen bromide with a compound of formulae (H') and (H"), respectively, in the presence of a protic solvent such as ethanol. The reaction is performed at a temperature in the region of 80°C.

More particularly, the carbamates of general formulae (1d') and (1d") may be obtained by reacting a chlorocarbonate of formula (O) (X = Cl) with a compound of general formulae (1c') and (1c"), for example in a solvent such as tetrahydrofuran, in the presence of a base such as sodium hydrogen carbonate, at a temperature in the region of 20°C.

More particularly, the carboxamides (1e') and (1e") may be obtained, respectively, from the amines of general formulae (Ic') and (1c")

- by reacting the amines (1c') and (1c") with an acid chloride of formula (P) (X = Cl), in the presence, for example, of a solvent such as pyridine, at a temperature in the region of 20°C;
- by reacting the amines (1c') and (1c") with an acid anhydride of formula (P) (X = OCOR7), in the presence, for example, of a solvent such as pyridine at a temperature in the region of 20°C;
- by coupling the amines (1c') and (1c") with an acid of formula (P) (X = OH) under the conditions described, for example, by D.D. DesMarteau; V. Montanari (Chem. Lett., 2000 (9). 1052), in the presence of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and in the presence of a base such as triethylamine, at a temperature in the region of 40°C.

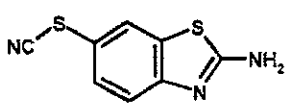
Scheme 2: Synthesis of benzothiazole derivatives of formulae (2a'), (2b'), (2c'), (2d'), (2a)', (2b'), (2c') and (2d')

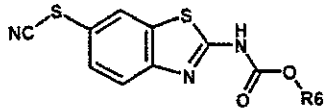


In Scheme 2 above, the substituent Ra may take the meanings indicated above for the products of formulae (I') and (I").

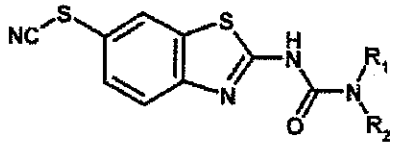
In Scheme 2 above, the groups CONR1R2, CO2R6 and COR7, which constitute W, may take values of W as defined above for the products of formulae (I') and (I"), when W≠H.

In Scheme 2 above, the benzothiazoles of general formulae (2a"), (2b"), (2c") and (2d") and the reduced analogues thereof of general formulae (2a'), (2b'), (2c') and (2d') may be prepared from 2-amino-1,3-benzothiazol-6-yl thiocyanate (K) (commercial compound).


K


L1

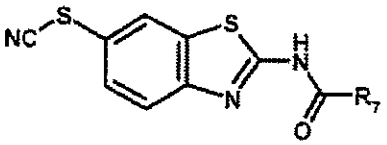
The carbamates of general formula (L1) may be obtained, for example, by reacting a chlorocarbonate of formula (O) (X = Cl) with 2-amino-1,3-benzothiazol-6-yl thiocyanate (K), in a solvent such as tetrahydrofuran, in the presence of a base such as sodium hydrogen carbonate, at a temperature in the region of 20°C.



L2

The compounds of general formula (L2) may be obtained, for example, by reacting the carbamates of formula (L1) in which R6 = phenyl with amines NHR1R2 of formula (R) (with R1 and R2 as defined above), in the presence of an aprotic solvent such as tetrahydrofuran, at a temperature in the region of 20°C.

The ureas (2b') and (2b") may be obtained, for example, respectively, from the carbamates (2a') and (2a") in which R6 = phenyl, in the same manner as the ureas (L2) are obtained by reacting amines on the carbamates of the type (L1).



L3

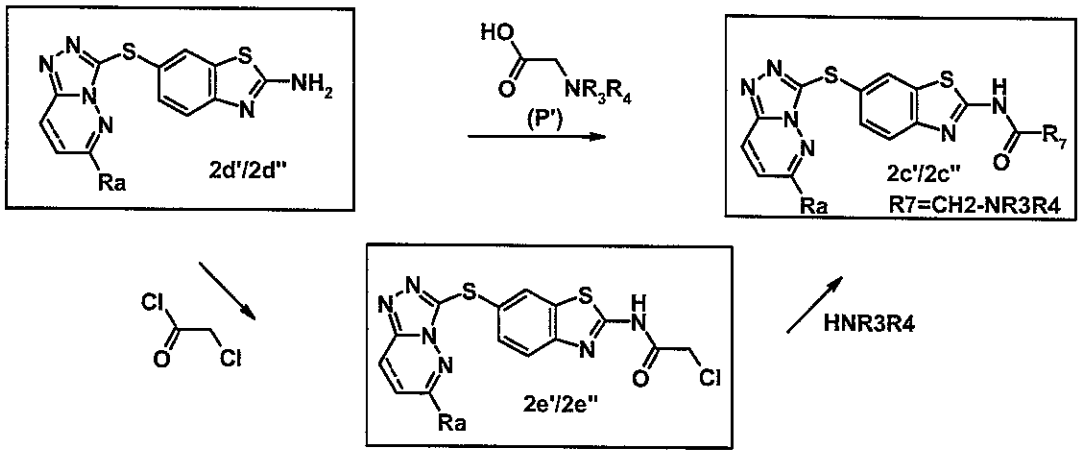
The compounds of general formula (L3) may be obtained, for example:

- by reacting an acid chloride of formula (P) (X = Cl) with 2-amino-1,3-benzothiazol-6-yl thiocyanate (K), in the presence, for example, of a solvent such as pyridine, at a temperature in the region of 20°C,
- by reacting an acid anhydride of formula (P) (X = OCOR7) with 2-amino-1,3-benzothiazol-6-yl thiocyanate (K), in the presence, for example, of a solvent such as pyridine, at a temperature in the region of 20°C,
- by coupling 2-amino-1,3-benzothiazol-6-yl thiocyanate (K) with an acid of formula (P) (X = OH) under the conditions described, for example, by D.D. DesMarteau; V. Montanari (Chem. Lett., 2000 (9).1052), in the presence of 1-

hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and in the presence of a base such as triethylamine, at a temperature in the region of 40°C.

In the same manner that the carboxamides (L3) may be obtained via acylation of the amine (K), the carboxamides (2c') and (2c") may be obtained, respectively, from the amines (2d') and (2d") by coupling with an acid of formula (P) (X = OH) under the conditions described, for example, by N. Xi et al., Bioorg. Med. Chem. Lett. 15 (2005) 5211–5217, in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), in a solvent such as N,N-dimethylformamide, in the presence of a base such as diisopropylethylamine, at a temperature in the region of 20°C.

Scheme 2bis: Routes for synthesizing the glycinamide derivatives (2c') and (2c")



In Scheme 2bis above, the substituent R7 may take the meaning of an aminomethyl group. These glycinamides (2c'/2c") may be obtained by coupling the amines (2d') and (2d") with a glycidic acid (P') using the methods described above for the acids (P) (X = OH).

The glycidic acids (P') may be prepared from bromoacetic acid and amines HNR3R4 under conditions similar to those described by D. T. Witiak *et al.*; J. Med. Chem. 1985, 28, 1228.

Alternatively, the amines (2d') and (2d") may be treated with fluoroacetyl chloride in the presence of a base such as pyridine, triethylamine or N-methylmorpholine, in a solvent such as dichloromethane at a temperature in the region of 0°C to 20°C. The α-chloroacetamides (2e'/2e") thus formed can react with amines of the type HNR3R4, as defined above, in a solvent such as pyridine at a temperature in the region of 20°C, to give the derivatives (2c'/2c") as defined in Scheme 2bis above.

The compounds of general formulae (M1), (M2) and (M3) may be obtained, for example, by reduction of compounds of general formula (L1), (L2) or (L3) with DL-dithiothreitol, in the presence of sodium hydrogen carbonate, in a solvent such as ethanol and at a temperature in the region of 80°C.

The compound of general formula (N) may be prepared *in situ* by reduction of the compound of formula (K), for example with sodium borohydride in a solvent such as N,N-dimethylformamide, in the presence of a base such as triethylamine and at a temperature in the region of 95°C or between 20°C and 95°C.

More particularly, the benzothiazoles of general formulae (2d') and (2d") may also be prepared, respectively, from carbamates of formulae (2a') and (2a") in which R6 = t-butyl, by reaction, for example, with trifluoroacetic acid in a solvent such as dichloromethane, at a temperature in the region of 20°C.

Reciprocally, the benzothiazoles of general formulae (2a') and (2a") may also be prepared from benzothiazoles of formulae (2d') and (2d"), respectively, for example, by reaction with a chlorocarbonate of formula (O) (X = Cl), in a

solvent such as tetrahydrofuran, in the presence of a base such as sodium hydrogen carbonate, at a temperature in the region of 20°C.

More particularly, the benzothiazoles of general formulae (2a"), (2b"), (2c") and (2d") and the reduced analogues thereof of general formulae (2a'), (2b'), (2c') and (2d') may be prepared, for example:

1) either by coupling a compound of formula (E) with derivatives (M1), (M2) and (M3) and (N) generated *in situ* by reduction of the derivatives (L1), (L2), (L3) and (K) with sodium borohydride, in a solvent such as N,N-dimethylformamide, and in the presence of a base such as triethylamine, at a temperature in the region of 95°C or between 50°C and 95°C;

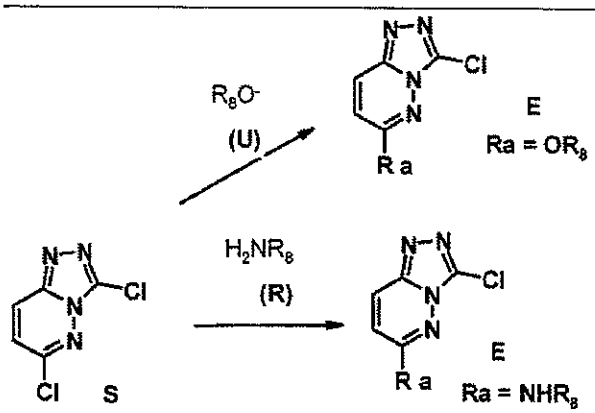
2) or by coupling the isolated derivatives (M1), (M2) and (M3) and a compound of formula (E), in the presence of sodium borohydride in a solvent such as N,N-dimethylformamide and in the presence of a base such as triethylamine, at a temperature in the region of 95°C;

3) or by coupling the isolated derivatives (M1), (M2) and (M3) and a compound of formula (E) under the conditions described, for example, by U. Schopfer et al. (Tetrahedron, 2001, 57, 3069) in the presence of n-tributylphosphine, potassium tert-butoxide, tris(dibenzylideneacetone)-dipalladium(0) and bis(2-diphenylphosphinophenyl) ether in a solvent such as toluene at a temperature in the region of 110°C;

4) or by coupling a compound of formula (E) with derivatives (M1), (M2) and (M3) and (N) generated *in situ* by reduction of the derivatives (L1), (L2), (L3) and (K) in the presence of DL-dithiothreitol and sodium hydrogen carbonate, in a solvent such as ethanol and at a temperature in the region of 80°C.

The reductive conditions 1) and 2) may give products of formulae (2a), (2b), (2c) and (2d) such that ---- represent a single or double bond, whereas conditions 3) and 4) give products of formulae (2a), (2b), (2c) and (2d) such that ---- represent a double bond.

Scheme 3: Routes for synthesizing triazolopyridazine derivatives of formula (E)



In Scheme 3 above, the substituent Ra has the meanings indicated above for the products of formulae (I') and (I").

The substituent R8 represents a cycloalkyl radical such as defined above for the products of formula (I).

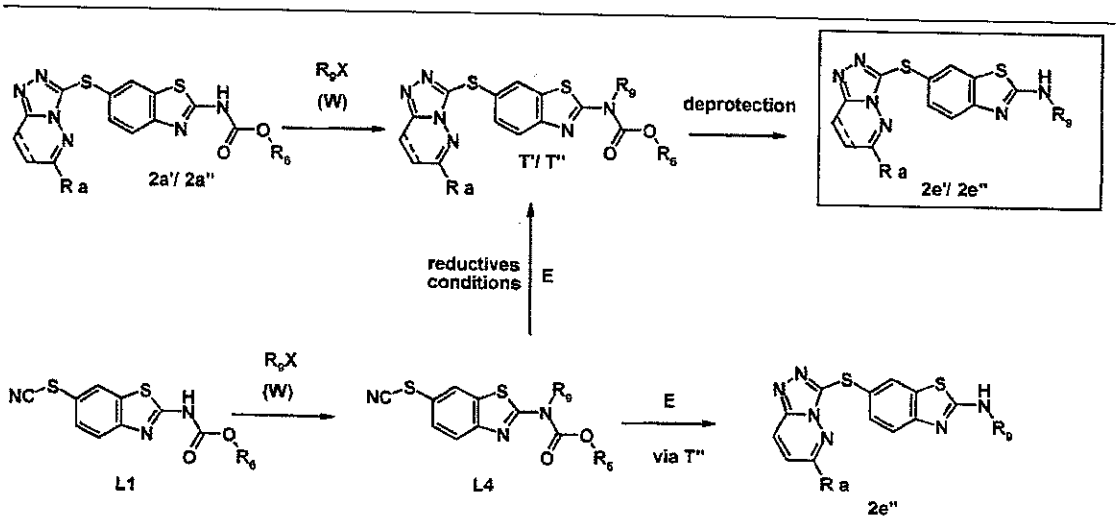
The compounds of formula (E) may be obtained, for example, as indicated in Scheme 3 above, from commercial 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine of formula (S).

More particularly, the compounds of formula (E) in which Ra represents a radical OR8 may be obtained by treating 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine (S) at a temperature in the region of 20°C to 80°C and in a solvent such as tetrahydrofuran with an alkoxide of formula (U), which is itself obtained by treating an alcohol (HOR8) with, for example, sodium hydride in a solvent such as tetrahydrofuran at a temperature in the region of 0°C to 20°C.

More particularly, the compounds of formula (E) where Ra represents an R8NH radical may be obtained by treating 3,6-dichloro[1,2,4]triazolo[4,3-b]-

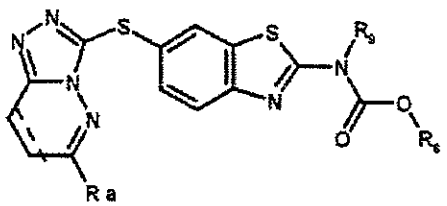
pyridazine (S) with an amine of formula (R8NH2), at a temperature in the region of 20°C to 50°C and in a solvent such as N,N-dimethylformamide.

Scheme 4: Synthesis of the benzothiazole derivatives of formulae (2e') and (2e")



According to Scheme 4 above, the benzothiazoles of general formulae (2e') and (2e") may be prepared, respectively, from the compounds of formulae (2a') and (2a").

In Scheme 4 above, the substituent OR6 preferentially represents O-t-butyl. The substituent R9 represents an alkyl or cycloalkyl radical optionally substituted with an alkoxy or heterocycloalkyl radical or NR3R4 (R3 and R4 as defined above).



T'/ T"

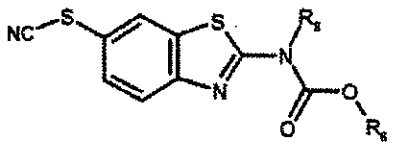
The carbamates of general formulae (T') and (T") may be obtained, respectively, by reacting carbamates of general formulae (2a') and (2a") with R6 = tBu, preferentially, for example with alkyl halides of formula (W), in a

solvent such as N,N-dimethylformamide, in the presence of sodium hydride, at a temperature of between 20 and 90°C.

The benzothiazoles of general formulae (2e') and (2e") may also be prepared from the compounds of formula (L1), with, preferably, R6 = tBu, via the compounds of formulae (T') and (T").

More particularly, the compounds of general formulae (2e') and (2e") may be obtained, respectively, by treating the isolated compounds (T') and (T"), for example, with trifluoroacetic acid, in a solvent such as dichloromethane, at a temperature in the region of 20°C.

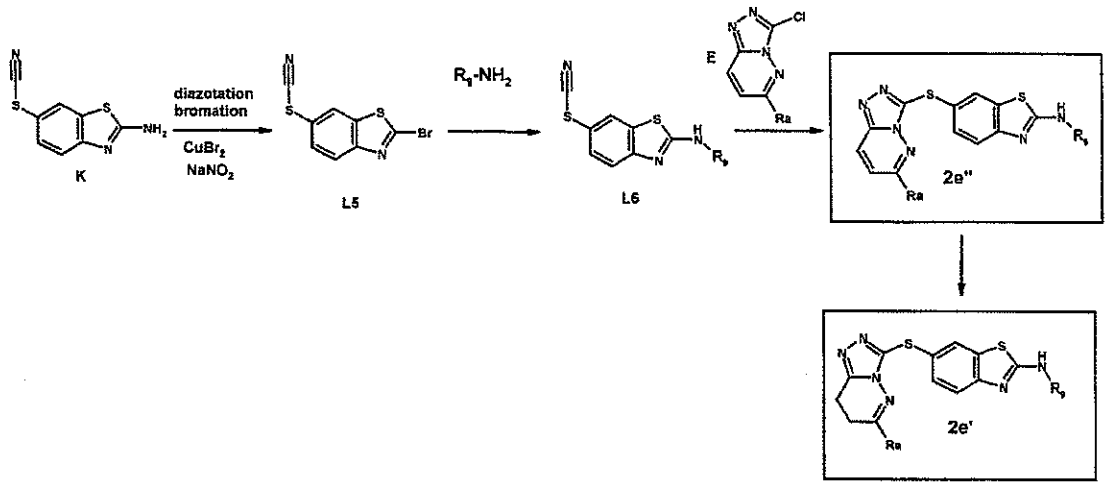
Alternatively, the compounds of general formula (2e") may be obtained directly by reacting the compounds of formulae (L4) and (E), via compound (T") formed *in situ*, for example in the presence of DL-dithiothreitol and sodium hydrogen carbonate, in a solvent such as ethanol and at a temperature in the region of 80°C, optionally followed by an *in situ* treatment with trifluoroacetic acid at 20°C, if necessary.



L4

The carbamates of general formula (L4) may be obtained by reacting carbamates of general formula (L1), for example, with alkyl halides of formula (W), in a solvent such as N,N-dimethylformamide, in the presence of sodium hydride, at a temperature of between 20 and 90°C.

Scheme 5: Synthesis of the benzothiazole derivatives of formulae (2e') and (2e")



Alternatively, according to Scheme 5 above, the benzothiazoles of general formula (2e") may be prepared from the compounds of formulae (L6) and (E), for example, in the presence of DL-dithiothreitol and sodium hydrogen carbonate, in a solvent such as ethanol and at a temperature in the region of 80°C.

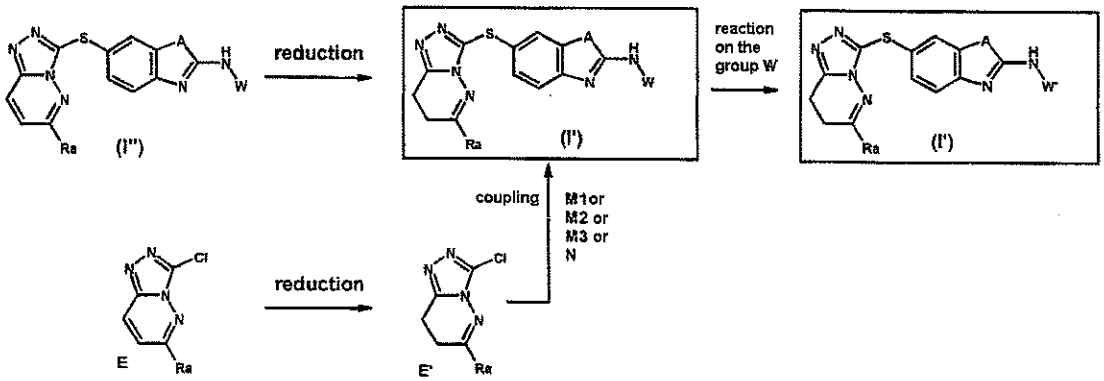
The benzothiazoles of general formula (2e') may be prepared from the compounds of formula (2e") according to the methods described below for the preparation of the compounds (I') from the compounds (I").

The compounds of formula (L6) may be prepared from the 2-bromobenzothiazole derivative (L5) by treatment with a derivative NH2R9, for example, in a solvent such as tetrahydrofuran, at a temperature in the region of 20°C.

The substituent R9 represents an alkyl or cycloalkyl radical optionally substituted with an alkoxy or heterocycloalkyl radical or NR3R4 (R3 and R4 as defined above).

The compounds of formula (L5) may be prepared from 2-amino-1,3-benzothiazol-6-yl thiocyanate (K) (commercial compound), for example, by treatment with an alkyl nitrite and cuprous bromide in a solvent such as acetonitrile, at a temperature in the region of 0-20°C, according to the method described by Jagabandhu Das *et al.* in J. Med. Chem. 2006, 49, 6819-6832.

Scheme 6: Other routes for synthesizing reduced derivatives of formula (I')



According to Scheme 6 above, the benzothiazoles of general formula (I') may also be prepared from the compounds of formula (I"), via reduction, for example, with sodium borohydride, in a solvent such as ethanol, at a temperature in the region of 80°C, or via reduction with zinc (0) in the presence of acetic acid, at a temperature in the region of 20°C.

Alternatively, the compounds (I') may also be prepared from the compounds of formula (E') by coupling with compounds of the type M1, M2, M3 or N, obtained as intermediates via reduction of the compounds L1, L2, L3 or K *in situ*, as described above in Scheme 2. The compounds of the type M1, M2 or M3 may also be isolated and used for the coupling with (E'). The compounds (E') may be obtained from the compounds of formula (E) by reduction, for example, with zinc (0) in the presence of acetic acid, at a temperature in the region of 20°C.

Alternatively, the compounds (I') may also be prepared from other compounds (I') via conversion of the group W into a group W' of the same

nature as defined above for W and according to the type of reaction defined in Scheme 2: conversion of 2d'/2d" into 2a'/2a" and into 2c'/2c", conversion of 2a'/2a" into 2d'/2d" and into 2b'/2b".

In the compounds of general formula (I) as defined above, the sulfur S can be oxidized to sulfoxide SO or sulfone SO2 according to the methods known to those skilled in the art, if necessary protecting any reactive groups with suitable protecting groups.

Among the starting materials of formulae J, K, O, P, Q, R, S, U, V and W, some are known and may be obtained either commercially or according to the usual methods known to those skilled in the art, for example from commercial products.

It is understood by those skilled in the art that, to implement the processes according to the invention described previously, it may be necessary to introduce protecting groups for the amino, carboxyl and alcohol functions in order to avoid side reactions.

The following non-exhaustive list of examples of protection of reactive functions may be mentioned:

- hydroxyl groups may be protected, for example, with alkyl radicals such as tert-butyl, trimethylsilyl, tert-butyldimethylsilyl, methoxymethyl, tetrahydropyranyl, benzyl or acetyl,
- amino groups may be protected, for example, with acetyl, trityl, benzyl, tert-butoxycarbonyl, BOC, benzyloxycarbonyl or phthalimido radicals or other radicals known in peptide chemistry.

Acid functions may be protected, for example, in the form of esters formed with readily cleavable esters such as benzyl or tert-butyl esters or esters known in peptide chemistry.

A list of various protecting groups that may be used will be found in the manuals known to those skilled in the art and, for example, in patent BF 2 499 995.

It may be noted that intermediate products or products of formula (I) thus obtained via the processes indicated above may be subjected, if desired and if necessary, in order to obtain other intermediates or other products of formula (I), to one or more transformation reactions known to those skilled in the art, for instance:

a) a reaction for esterification of an acid function,

b) a reaction for saponification of an ester function to an acid function,

c) a reaction for reduction of the free or esterified carboxyl function to an alcohol function,

d) a reaction for conversion of an alkoxy function into a hydroxyl function, or alternatively of a hydroxyl function into an alkoxy function,

e) a reaction for removal of the protecting groups that may be borne by protected reactive functions,

f) a salification reaction with a mineral or organic acid or with a base to obtain the corresponding salt,

g) a reaction for resolution of racemic forms into resolved products,

the said products of formula (I) thus obtained being in any possible racemic, enantiomeric or diastereoisomeric isomer form.

Reactions a) to g) may be performed under the usual conditions known to those skilled in the art, for instance those indicated hereinbelow.

a) The products described above may, if desired, undergo, on the possible carboxyl functions, esterification reactions that may be performed according to the usual methods known to those skilled in the art.

b) The possible conversions of ester functions into an acid function of the products described above may, if desired, be performed under the usual conditions known to those skilled in the art, especially by acidic or alkaline hydrolysis, for example with sodium hydroxide or potassium hydroxide in alcoholic medium, for instance in methanol, or alternatively with hydrochloric acid or sulfuric acid.

The saponification reaction may be performed according to the usual methods known to those skilled in the art, for instance in a solvent such as methanol, ethanol, dioxane or dimethoxyethane, in the presence of sodium hydroxide or potassium hydroxide.

c) The possible free or esterified carboxyl functions of the products described above may, if desired, be reduced to an alcohol function via the methods known to those skilled in the art: the possible esterified carboxyl functions may, if desired, be reduced to an alcohol function via the methods known to those skilled in the art and especially with lithium aluminium hydride in a solvent such as, for example, tetrahydrofuran, dioxane or ethyl ether.

The possible free carboxyl functions of the products described above may, if desired, be reduced to an alcohol function especially with boron hydride.

d) The possible alkoxy functions, especially such as methoxy, of the products described above may be, if desired, converted into a hydroxyl function under the usual conditions known to those skilled in the art, for example with boron tribromide in a solvent such as, for example, methylene chloride, with pyridine hydrobromide or hydrochloride, or alternatively with hydrobromic acid or hydrochloric acid in water or trifluoroacetic acid at reflux.

e) The removal of the protecting groups such as, for example, those indicated above may be performed under the usual conditions known to those skilled in

the art, especially via acidic hydrolysis performed with an acid such as hydrochloric acid, benzenesulfonic acid or para-toluenesulfonic acid, formic acid or trifluoroacetic acid, or alternatively via catalytic hydrogenation.

The phthalimido group may be removed with hydrazine.

f) The products described above may, if desired, undergo salification reactions, for example with a mineral or organic acid or with a mineral or organic base according to the usual methods known to those skilled in the art: such a salification reaction may be performed, for example, in the presence of hydrochloric acid, for example, or tartaric acid, citric acid or methanesulfonic acid, in an alcohol, for instance ethanol or methanol.

g) The possible optically active forms of the products described above may be prepared by resolving racemic mixtures according to the usual methods known to those skilled in the art.

The products of formula (I) as defined above and the acid-addition salts thereof have advantageous pharmacological properties especially on account of their kinase-inhibiting properties as indicated above.

The products of the present invention are especially useful for treating tumours.

The products of the invention may thus also increase the therapeutic effects of commonly used antitumour agents.

These properties justify their therapeutic use, and a subject of the invention is particularly, as medicaments, the products of formula (I) as defined above, the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with

pharmaceutically acceptable mineral and organic acids or with pharmaceutically acceptable mineral and organic bases of the said products of formula (I).

A subject of the invention is most particularly, as medicaments, the products corresponding to the following formulae:

- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- 1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea
- N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- N-[6-({6-[(trans-4-hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- 1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide

- phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea
- 6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-N-[2-(pyrrolidin-1-yl)ethyl]-1,3-benzothiazol-2-amine
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-methoxyacetamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2,N^2-dimethylglycinamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methylbutanamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide
- 6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine
- N-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- N-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- 6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine
- N-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- trans-4-{[3-({2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}-sulfanyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]amino}cyclohexyl cyclopropanecarboxylate
- N-[6-({6-[(trans-4-hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]acetamide
- 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclopropyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine

- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2,N^2-dimethylglycinamide
- 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclohexyl-7,8-dihydro[1,2,4]-triazolo[4,3-b]pyridazin-6-amine
- ethyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate
- 2-chloro-N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2-cyclopropylglycinamide
- 6-[(6-{[4-(trifluoromethyl)cyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-amine
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2,N^2-diethylglycinamide
- N-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- 1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[3-(morpholin-4-yl)propyl]urea
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[3-(morpholin-4-yl)propyl]urea
- 1-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-[2-(morpholin-4-yl)ethyl]-3-{6-[(6-{[4-(trifluoromethyl)cyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}urea

- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-cyclopropylacetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- rac-cis/trans-N-{4-[(3-{[2-({[2-(morpholin-4-yl)ethyl]carbamoyl}amino)-1,3-benzothiazol-6-yl]sulfanyl}[1,2,4]triazolo[4,3-b]pyridazin-6-yl)oxy]cyclohexyl}-acetamide
- N-{6-[(6-{[4-(trifluoromethyl)cyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- 1-[6-({6-[(trans-4-hydroxycyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}-sulfanyl)-1,3-benzothiazol-2-yl]-3-[2-(morpholin-4-yl)ethyl]urea
- 6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine
- 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclobutyl[1,2,4]triazolo[4,3-b]-pyridazin-6-amine
- N-(6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)cyclobutanecarboxamide
- rac-6-({6-[(trans-2-fluorocyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}-sulfanyl)-1,3-benzothiazol-2-amine
- rac-N-{6-[(6-{[(trans-2-fluorocyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- N-(6-{[6-(cyclobutylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- N-(6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- rac-N^2,N^2-diethyl-N-[6-({6-[(trans-2-fluorocyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]glycinamide
- rac-2-(4-ethylpiperazin-1-yl)-N-{6-[(6-{[trans-2-fluorocyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}acetamide
- rac-N-{6-[(6-{[trans-2-fluorocyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-2-(morpholin-4-yl)acetamide

- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(morpholin-4-yl)acetamide
- rac-2-(4-cyclopropylpiperazin-1-yl)-N-{6-[(6-{[trans-2-fluorocyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(4-cyclopropylpiperazin-1-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(1,1-dioxidothiomorpholin-4-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(1,4-oxazepan-4-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(3,3-difluoropiperidin-1-yl)acetamide
- rac-cis/trans-1-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea
- rac-cis/trans-N-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- rac-cis/trans-1-[6-({6-[(4-methylcyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(piperidin-1-yl)azetidine-1-carboxamide
- rac-cis/trans-N-[6-({6-[(4-methylcyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(morpholin-4-yl)azetidine-1-carboxamide
- rac-N-{6-[(6-{[trans-2-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide

- rac-1-{6-[(6-{[trans-2-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxyazetidine-1-carboxamide
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-oxetan-3-ylurea
- rac-cis/trans-1-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea
- rac-cis/trans-N-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide

and also the addition salts with pharmaceutically acceptable mineral and organic acids or with pharmaceutically acceptable mineral and organic bases of the said products of formula (I).

The invention also relates to pharmaceutical compositions containing, as active principle, at least one of the products of formula (I) as defined above or a pharmaceutically acceptable salt of this product or a prodrug of this product and, where appropriate, a pharmaceutically acceptable support.

The invention thus covers pharmaceutical compositions containing, as active principle, at least one of the medicaments as defined above.

Such pharmaceutical compositions of the present invention may also, where appropriate, contain active principles of other antimitotic medicaments, especially such as those based on taxol, cisplatin, DNA-intercalating agents and the like.

These pharmaceutical compositions may be administered orally, parenterally or locally as a topical application to the skin and mucous membranes or via intravenous or intramuscular injection.

These compositions may be solid or liquid and may be in any pharmaceutical form commonly used in human medicine, for instance simple or sugar-coated tablets, pills, lozenges, gel capsules, drops, granules, injectable preparations, ointments, creams or gels; they are prepared according to the usual methods. The active principle may be incorporated therein with excipients usually used in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or plant origin, paraffin derivatives, glycols, various wetting agents, dispersants or emulsifiers, and preserving agents.

The usual dosage, which is variable according to the products used, the patient treated and the complaint under consideration, may be, for example, from 0.05 to 5 g per day or preferably from 0.1 to 2 g per day for an adult.

A subject of the present invention is also the use of the products of formula (I) as defined above or of pharmaceutically acceptable salts of these products for the preparation of a medicament for inhibiting the activity of a kinase protein.

A subject of the present invention is also the use of products of formula (I) as defined above for the preparation of a medicament for treating or preventing a disease characterized by deregulation of the activity of a kinase protein.

Such a medicament may especially be intended for treating or preventing a disease in a mammal.

A subject of the present invention is also the use defined above, in which the kinase protein is a tyrosine kinase protein.

A subject of the present invention is also the use defined above, in which the tyrosine kinase protein is MET or mutant forms thereof.

A subject of the present invention is also the use defined above, in which the kinase protein is in a cell culture.

A subject of the present invention is also the use defined above, in which the kinase protein is in a mammal.

A subject of the present invention is especially the use of a product of formula (I) as defined above for the preparation of a medicament for preventing or treating diseases associated with an uncontrolled proliferation.

A subject of the present invention is particularly the use of a product of formula (I) as defined above for the preparation of a medicament for treating or preventing a disease chosen from the following group: blood vessel proliferation disorders, fibrotic disorders, "mesangial" cell proliferation disorders, metabolic disorders, allergies, asthmas, thromboses, nervous system diseases, retinopathy, psoriasis, rheumatoid arthritis, diabetes, muscle degeneration and cancers.

A subject of the present invention is thus most particularly the use of a product of formula (I) as defined above for the preparation of a medicament for treating or preventing oncology diseases and especially for treating cancers.

Among these cancers, attention is focused on the treatment of solid or liquid tumours and the treatment of cancers that are resistant to cytotoxic agents.

The cited products of the present invention may be used especially for treating primary tumours and/or metastases, in particular in stomach, liver, kidney, ovarian, bowel or prostate cancer, lung cancer (NSCLC and SCLC), glioblastomas, thyroid, bladder or breast cancers, melanomas, lymphoid or

myeloid haematopoietic tumours, sarcomas, brain cancers, cancer of the larynx, cancer of the lymphatic system, bone cancers and pancreatic cancers.

A subject of the present invention is also the use of the products of formula (I) as defined above for the preparation of medicaments intended for cancer chemotherapy.

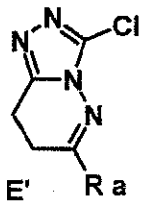
Such medicaments intended for cancer chemotherapy may be used alone or in combination.

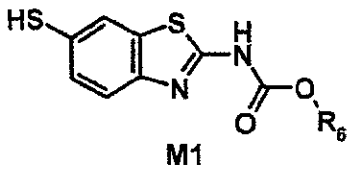
The products of the present patent application may especially be administered alone or in combination with chemotherapy or radiotherapy or alternatively in combination, for example, with other therapeutic agents.

Such therapeutic agents may be commonly used antitumour agents.

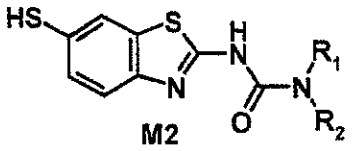
Kinase inhibitors that may be mentioned include butyrolactone, flavopiridol and 2-(2-hydroxyethylamino)-6-benzylamino-9-methylpurine, known as olomoucine.

A subject of the present invention is also, as novel industrial products, the synthetic intermediates of formulae E', M1, M2, M3 and N as defined above and recalled hereinbelow:

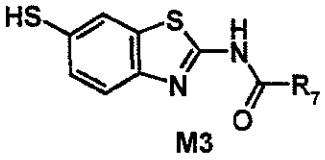




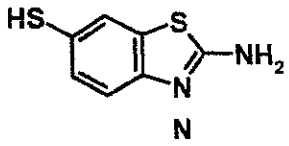
M1



M2



M3



N

in which the groups CONR1R2, CO2R6 and COR7, which constitute W, may take the values of W as defined above for the products of formula (I), when W≠H, and the substituent Ra may take the meanings indicated above for the products of formula (I).

The examples that follow, which are products of formula (I), illustrate the invention without, however, limiting it.

Experimental section

The nomenclature of the compounds of the present invention was produced with the ACDLABS software version 10.0 and version 11

Microwave oven used:

Biotage, Initiator EXP-EU, 300 W max, 2450 MHz

The 400 MHz and 300 MHz 1H NMR spectra were acquired using a Brüker Avance DRX-400 or Brüker Avance DPX-300 spectrometer with the chemical shifts (δ in ppm) in the solvent dimethyl sulfoxide-d_6 (DMSO-d_6) referenced to 2.5 ppm, at a temperature of 303 K.

The Mass spectra were acquired either by analysis:

- LC-MS-DAD-ELSD (MS = Waters ZQ)
- LC-MS-DAD-ELSD (MS = Platform II Waters Micromass)
- UPLC-MS-DAD-ELSD (MS = Quattro Premier XE Waters)
- UPLC-SQD (Waters)

DAD wavelength considered λ = 210-400 nm

ELSD: Sedere SEDEX 85; nebulization temperature = 35°C; nebulization pressure = 3.7 bar

Example 1:

N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide

a) N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide may be prepared in the following manner:

75 mg of 6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine and 20 µL of cyclopropanecarboxylic acid chloride are added to 2 cm^3 of pyridine at 20°C. After 3 hours, a further 20 µL of cyclopropanecarboxylic acid chloride are added and and the mixture is stirred for 18 hours. A further 20 µL of cyclopropanecarboxylic acid chloride are added and the mixture is left to react for a further one hour. The reaction mixture is concentrated to dryness and the solid residue is chromatographed by solid deposition on a Biotage Quad cartridge 12/25 (KP-SIL, 60A; 32-63 µM), eluting with a 99.5/0.5 to 90/10 gradient of dichloromethane/methanol. The solid obtained is washed with ethyl ether. 66 mg of N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 0.88 - 1.01 (m, 4 H) 1.13 - 1.53 (m, 6 H) 1.52 - 1.66 (m, 2 H) 1.71 - 1.86 (m, 2 H) 1.92 - 2.04 (m, 1 H)

4.61 - 4.74 (m, 1 H) 7.02 (d, *J* = 10.0 Hz, 1 H) 7.41 (dd, *J* = 8.0, 2.0 Hz, 1 H) 7.67 (d, *J* = 8.0 Hz, 1 H) 8.05 (d, *J* = 2.0 Hz, 1 H) 8.28 (d, *J* = 10.0 Hz, 1 H) 12.67 (br. s., 1H)

MASS SPECTRUM: UPLC-SQD: MH+ m/z = 467+; MH- = 465-.

b) 6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine may be prepared in the following manner:

A stream of argon is bubbled through a solution of 149 mg of 2-amino-1,3-benzothiazol-6-yl thiocyanate (commercial) in 20 cm^3 of ethanol for 5 minutes. 4 mg of potassium dihydrogen phosphate in 0.2 cm^3 of water, 333 mg of DL-dithiothreitol and 182 mg of 3-chloro-6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]-pyridazine are then added. The reaction mixture is heated at 80°C for 23 hours and then concentrated to dryness under vacuum. The residue is purified on silica by solid deposition, eluting with a gradient of from 100% dichloromethane to 80/20 dichloromethane/(38 dichloromethane/17 methanol/2 aqueous ammonia). 130 mg of 6-{[6-(cyclohexyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine are thus obtained in the form of a yellowish powder, the characteristics of which are as follows:

MASS SPECTRUM: LC/MS Electrospray on WATERS UPLC - SQD:
MH+ m/z = 399+; MH-= 397-

c) 3-Chloro-6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazine may be prepared in the following manner:

762 mg of sodium hydride at 60% in oil are added to a solution of 3.18 g of cyclohexanol in 30 cm^3 of tetrahydrofuran at 0°C under argon. After stirring for 15 minutes, 3 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine (commercial) are added. The brown suspension is stirred for 22 hours while allowing it to return gradually to 20°C. The reaction medium is then poured into ice-water and the mixture is extracted with ethyl acetate. After concentrating the organic phase to dryness under vacuum, a brown oil is obtained. The oily residue is chromatographed on a Biotage Quad 12/25 cartridge (KP-SIL, 60 Å;

32-63 µM), eluting with a 95/5 to 65/35 cyclohexane/ethyl acetate gradient. 2.7 g of 3-chloro-6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazine are thus obtained in the form of a yellowish powder, the characteristics of which are as follows:

MASS SPECTRUM: LC/MS Electrospray on WATERS UPLC - SQD:
MH+ = 253+

Example 2:

1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea

a) 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea may be prepared in the following manner:

A stream of argon is bubbled through a solution of 339 mg of 1-[2-(morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea in 20 cm^3 of ethanol for 5 minutes. 5 mg of potassium dihydrogen phosphate in 0.2 cm^3 of water, 463 mg of DL-dithiothreitol and 253 mg of 3-chloro-6-(cyclohexyloxy)[1,2,4]-triazolo[4,3-b]pyridazine (**1c**) are then added. The reaction mixture is then heated at 80°C for 47 hours, and the whitish solution is then evaporated to dryness under vacuum. The residue is purified on silica by solid deposition, eluting with a gradient of from 100% dichloromethane to 85/15 dichloromethane/(38 dichloromethane/17 methanol/2 aqueous ammonia). 246 mg of 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-d_6) **δ** ppm 1.00 - 1.55 (m, 6 H) 1.62 (m, 2 H) 1.73 - 1.90 (m, 2 H) 2.29 - 2.47 (m, 6 H) 3.19 - 3.28 (m, 2 H) 3.59 (m, 4 H) 4.57 - 4.80 (m, 1 H) 6.77 (br. s., 1 H) 7.02 (d, *J* = 9.8 Hz, 1H) 7.36 (dd, *J* = 8.5, 1.5 Hz, 1 H) 7.54 (d, *J* = 8.5 Hz, 1 H) 7.99 (d, *J* = 1.5 Hz, 1 H) 8.27 (d, *J* = 9.8 Hz, 1 H) 10.90 (br. s., 1 H)

MASS SPECTRUM: UPLC-SQD: MH+ m/z = 555+; MH- = 553-

b) 1-[2-(Morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea may be prepared in the following manner:

A stream of argon is bubbled for 5 minutes through a mixture of 900 mg of 2-{[(2-morpholin-4-ylethyl)carbamoyl]amino}-1,3-benzothiazol-6-yl thiocyanate and 40 cm^3 of ethanol at 20°C. 11 mg of potassium dihydrogen phosphate in 0.4 cm^3 of water and 1.1 g of DL-dithiothreitol are then added. The mixture is heated at 80°C for 3.5 hours. The reaction medium is cooled to 20°C and then poured into water. The suspension is stirred for 45 minutes while maintaining gentle bubbling with argon. The precipitate formed is filtered off by suction and washed with 3×10 cm^3 of water and then dried under vacuum at 20°C. 633 mg of 1-(2-morpholin-4-ylethyl)-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea are thus obtained in the form of a white solid, the characteristics of which are as follows:

MASS SPECTRUM: LC-MS-DAD-ELSD: MH+ m/z = 339+; (M-H)- = 337-

c) 2-{[(2-Morpholin-4-ylethyl)carbamoyl]amino}-1,3-benzothiazol-6-yl thiocyanate may be prepared in the following manner:

0.44 cm^3 of 2-morpholin-4-ylethanamine is added at 20°C to a solution of 1 g of phenyl (6-thiocyanato-1,3-benzothiazol-2-yl)carbamate in 30 cm^3 of tetrahydrofuran at 20°C. After 24 hours, the reaction mixture is evaporated to dryness and the residue obtained is chromatographed on a Merck 70g cartridge (solid deposition; elution with a gradient of dichloromethane and then 90/10 dichloromethane/methanol). 902 mg of 2-{[(2-morpholin-4-ylethyl)carbamoyl]amino}-1,3-benzothiazol-6-yl thiocyanate are thus recovered in the form of a colourless foam, the characteristics of which are as follows:

MASS SPECTRUM: UPLC-MS-DAD-ELSD: MH+ m/z = 364+

d) Phenyl (6-thiocyanato-1,3-benzothiazol-2-yl)carbamate was prepared in the following manner:

7.5 g of phenyl chlorocarbonate and then 4.05 g of sodium hydrogen carbonate and 9.4 cm^3 of water are added, at 20°C, to a solution of 2.5 g of commercial 2-amino-1,3-benzothiazol-6-yl thiocyanate in 94 cm^3 of

tetrahydrofuran. The resulting mixture is then stirred at 20°C for 20 hours and then extracted with 2×150 cm^3 of ethyl acetate. The organic phases are combined and then washed with 3×50 cm^3 of saturated aqueous sodium hydrogen carbonate solution. The organic phase obtained is dried over magnesium sulfate and then concentrated to dryness under reduced pressure. The residue is taken up in 50 cm^3 of water and then filtered off by suction and dried under vacuum at 20°C. 3.45 g of phenyl (6-thiocyanato-1,3-benzothiazol-2-yl)carbamate are thus obtained in the form of a pale yellow solid, the characteristics of which are as follows:

MASS SPECTRUM: LC-MS-DAD-ELSD: MH+ m/z = 328+; (M-H)- =326-

Example 3:

N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide may be prepared in the following manner:

0.276 cm^3 of acetic anhydride and 160 mg of 6-{[6-(cyclohexyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine **(1b)** are added to 2 cm^3 of pyridine at 20°C. After 5 hours, a further 0.3 cm^3 of acetic anhydride is added and the mixture is left stirring for 17 hours. The reaction mixture is concentrated to dryness under vacuum. The yellowish solid residue is chromatographed on a Biotage Quad 12/25 cartridge (KP-SIL, 60 Å; 32-63 µM), eluting with a gradient of from 100% dichloromethane to 97.5/2.5 dichloromethane/methanol. 123 mg of N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo-[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ**ppm 1.05 - 1.53 (m, 6 H) 1.52 - 1.68 (m, 2 H) 1.71 - 1.85 (m, 2 H) 2.19 (s, 3 H) 4.56 - 4.73 (m, 1 H) 7.02 (d, *J*=10.0 Hz, 1 H) 7.40 (dd, *J*=8.5, 2.0 Hz, 1 H) 7.66 (d, *J*=8.5 Hz, 1 H) 8.06 (d, *J*=2.0 Hz, 1 H) 8.28 (d, *J*=10.0 Hz, 1 H) 12.37 (br. s, 1 H)

MASS SPECTRUM: UPLC-SQD: MH+ m/z=441+; MH- =439-

Example 4:

phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)carbamate

Phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate may be prepared in the following manner:

0.13 cm^3 of phenyl chlorocarbonate is added to 200 mg of 6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**1b**) in 5 cm^3 of pyridine, at 20°C. After 4 hours, the yellow suspension is concentrated to dryness under vacuum. The residue is chromatographed on a Biotage Quad 12/25 cartridge (KP-SIL, 60 Å; 32-63 µM), eluting with a gradient of from 100% dichloromethane to 92.5/7.5 dichloromethane/ methanol. 224 mg of phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.13 - 1.42 (m, 5 H) 1.43 - 1.66 (m, 3 H) 1.72 - 1.85 (m, 2 H) 4.63 - 4.74 (m, 1 H) 7.03 (d, *J*=10.0 Hz, 1 H) 7.25 - 7.35 (m, 3 H) 7.40 - 7.50 (m, 3 H) 7.69 (d, *J*=9.0 Hz, 1 H) 8.07 (d, *J*=2.0 Hz, 1 H) 8.28 (d, *J*=10.0 Hz, 1 H) 12.66 (br. s, 1 H)

MASS SPECTRUM: UPLC-SQD: MH+ m/z=519+; MH- =517-

Example 5:

1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea

a) 1-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea may be prepared in the following manner:

0.06 cm^3 of 2-(pyrrolidin-1-yl)ethanamine and 0.14 cm^3 of triethylamine are added to a solution of 200 mg of phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo-[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate (**4**) in 5 cm^3 of

tetrahydrofuran at 20°C. After 2 hours at 20°C, the reaction medium is heated at 60°C for 3 hours. The yellow solution is evaporated to dryness under reduced pressure. The residue is chromatographed on a Biotage Quad 12/25 cartridge (KP-SIL, 60 Å; 32-63 µM), eluting with a 99/1 to 50/50 dichloromethane/methanol gradient. 171 mg of 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.08 - 1.87 (m, 14 H) 2.52 - 2.63 (masked m, 6 H) 3.32 - 3.38 (masked m, 2 H) 4.57 - 4.80 (m, 1 H) 6.82 (br. s, 1 H) 7.02 (d, *J*=10.0 Hz, 1 H) 7.36 (dd, *J*=8.5, 2.0 Hz, 1 H) 7.55 (d, *J*=8.5 Hz, 1 H) 8.00 (d, *J*=2.0 Hz, 1 H) 8.27 (d, *J*=10.0 Hz, 1 H) 10.78 (s, 1 H)

MASS SPECTRUM: UPLC-SQD: MH+ m/z=539+; MH- =537-

Example 6:

6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-N-[2-(pyrrolidin-1-yl)ethyl]-1,3-benzothiazol-2-amine

a) 6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-N-[2-(pyrrolidin-1-yl)ethyl]-1,3-benzothiazol-2-amine may be prepared in the following manner:

686 mg of 2-(pyrrolidin-1-yl)ethanamine are added to a solution of 534 mg of 2-bromo-1,3-benzothiazol-6-yl thiocyanate in 7 cm^3 of tetrahydrofuran. The reaction medium is stirred for 18 hours at 20°C, and the suspension is then concentrated to dryness under reduced pressure. The oily brown residue obtained is taken up in 20 cm^3 of ethanol. The mixture is degassed by sparging with argon for 5 min at 20°C, and 5 mg of potassium dihydrogen phosphate in 0.2 cm^3 of water are then added, followed by addition of 617 mg of DL-Dithiothreitol and 253 mg of 3-chloro-6-(cyclohexyloxy)[1,2,4]triazolo-[4,3-b]pyridazine (1c). After 23 hours at reflux, the red suspension is concentrated to dryness under reduced pressure. The residue is purified by dry deposition on Biotage Quad 25M (KP-SIL, 60 Å; 32-63 µM), eluting with a

gradient of 95/5 to 85/15 of dichloromethane/(dichloromethane: 38/methanol: 17/aqueous ammonia: 2). The yellow solid obtained is washed with ether and pentane. 218 mg of 6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-N-[2-(pyrrolidin-1-yl)ethyl]-1,3-benzothiazol-2-amine are thus obtained in the form of a yellow powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.17 - 1.59 (m, 7 H) 1.60 - 1.73 (m, 7 H) 1.79 - 1.94 (m, 2 H) 2.45 (masked m, 2 H) 2.55 - 2.71 (m, 2H) 3.47 (q, *J*=6.0 Hz, 2 H) 4.68 - 4.81 (m, 1 H) 7.01 (d, *J*=10.0 Hz, 1 H) 7.24 - 7.35 (m, 2 H) 7.82 (d, *J*=1.5 Hz, 1 H) 8.15 (t, 1 H) 8.25 (d, *J*=10.0 Hz, 1

MASS SPECTRUM: UPLC-SQD: MH+ m/z=496+; MH- =494-

b) 2-Bromo-1,3-benzothiazol-6-yl thiocyanate may be prepared in the following manner:

A solution of 6.5 g of cuprous bromide in 666 cm^3 of acetonitrile is purged with argon for 5 min. The resulting solution is cooled to 0-5°C, and 4.3 cm^3 of tert-butyl nitrite are then added. 5 g of 2-amino-1,3-benzothiazol-6-yl thiocyanate (commercial) are then introduced portionwise, at 0°C. The reaction mixture is stirred for 3 hours at 20°C and then concentrated to dryness under reduced pressure. The residue is taken up in ethyl acetate and the solution obtained is then washed with saturated sodium bicarbonate solution. The organic phase is dried over magnesium sulfate and then concentrated to dryness under vacuum. 5.05 g of 2-bromo-1,3-benzothiazol-6-yl thiocyanate are thus obtained in the form of a golden-yellow powder, the characteristics of which are as follows:

MASS SPECTRUM: UPLC-SQD: MH+ m/z=271+

Example 7:

N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-methoxyacetamide

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-methoxyacetamide may be prepared in a manner similar

to that of Example **1a**, but starting with 200 mg of 6-{[6-(cyclohexyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**1b**) in 5 cm^3 of pyridine with 0.165 cm^3 of methoxyacetyl chloride after reaction for 23 hours at 20°C. 196 mg of N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-methoxyacetamide are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.09 - 1.40 (m, 5 H) 1.41 - 1.65 (m, 3 H) 1.72 - 1.86 (m, 2 H) 3.36 (s, 3 H) 4.19 (s, 2 H) 4.61 - 4.72 (m, 1 H) 7.02 (d, *J*=10.0 Hz, 1 H) 7.41 (dd, *J*=8.5, 2.0 Hz, 1 H) 7.68 (d, *J*=8.5 Hz, 1 H) 8.07 (d, *J*=2.0 Hz, 1 H) 8.28 (d, *J*=10.0 Hz, 1 H) 12.32 (br. s, 1 H)

MASS SPECTRUM: UPLC-SQD: MH+ m/z=469+; MH- =471-

Example 8:

N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²,N²-dimethylglycinamide

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²,N²-dimethylglycinamide may be prepared in a manner similar to that of Example **1a**, but starting with 100 mg of 6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**1b**) in 10 cm^3 of dichloromethane with 300 mg of N,N-dimethylglycyl chloride, 0.33 cm^3 of triethylamine and 11 mg of 4-N,N-dimethylaminopyridine, after reaction for 27 hours at 20°C. 75 mg of N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²,N²-dimethylglycinamide are thus obtained in the form of a yellowish powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.10 - 1.64 (m, 8 H) 1.69 - 1.87 (m, 2 H) 2.29 (s, 6 H) 3.37 - 3.52 (m, 2 H) 4.52 - 4.75 (m, 1 H) 7.02 (d, *J*=10.0 Hz, 1 H) 7.41 (dd, *J*=8.5, 2.0 Hz, 1 H) 7.67 (d, *J*=8.5 Hz, 1 H) 8.07 (d, *J*=2.0 Hz, 1 H) 8.28 (d, *J*=10.0 Hz, 1 H) 11.92 (br. s, 1 H)

MASS SPECTRUM: Waters-ZQ: MH+ m/z=484+; MH- =482-

Example 9:

N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methylbutanamide

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methylbutanamide may be prepared in a manner similar to that of Example **1a**, but starting with 102 mg of 6-{[6-(cyclohexyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine **(1b)** in 5 cm^3 of pyridine with 0.437 cm^3 of 3-methylbutanoyl chloride after reaction for 46 hours at 20°C. 98 mg of N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyrid-azin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methylbutanamide are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 0.93 (d, *J*=6.8 Hz, 6 H) 1.08 - 1.63 (m, 8 H) 1.71 - 1.82 (m, 2 H) 2.03 - 2.17 (m, 1 H) 2.36 (d, *J*=7.1 Hz, 2 H) 4.56 - 4.69 (m, 1 H) 7.02 (d, *J*=9.8 Hz, 1 H) 7.40 (dd, *J*=8.4, 1.8 Hz, 1 H) 7.66 (d, *J*=8.6 Hz, 1 H) 8.07 (d, *J*=2.0 Hz, 1 H) 8.28 (d, *J*=9.8 Hz, 1 H) 12.34 (br. s, 1 H)

MASS SPECTRUM: UPLC-SQD: MH+ m/z=483+; MH- =481-

Example 10:

N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide may be prepared in a manner similar to that of Example **1a**, but starting with 146 mg of 6-{[6-(cyclo-hexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine **(1b)** in 5 cm^3 of pyridine with 0.191 cm^3 of 3-methoxypropanoyl chloride after reaction for 23 hours at 20°C. 132 mg of N-(6-{[6-(cyclo-hexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-

methoxypropanamide are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.11 - 1.65 (m, 8 H) 1.74 - 1.83 (m, 2 H) 2.72 (t, *J*=6.1 Hz, 2 H) 3.23 (s, 3 H) 3.64 (t, *J*=6.1 Hz, 2 H) 4.62 - 4.72 (m, 1 H) 7.02 (d, *J*=9.8 Hz, 1 H) 7.41 (dd, *J*=8.3, 2.0 Hz, 1 H) 7.66 (d, *J*=8.6 Hz, 1 H) 8.06 (d, *J*=2.0 Hz, 1 H) 8.28 (d, *J*=9.8 Hz, 1 H) 12.37 (br. s, 1 H)

MASS SPECTRUM: Waters-ZQ: MH+ m/z=485+; MH- =483-

Example 11:

6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine

a) 6-{[6-(Cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine may be prepared in a manner similar to that of Example **1b**, but starting with 889 mg of 3-chloro-6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazine in 30 cm^3 of degassed ethanol, 17 mg of potassium dihydrogen phosphate in 0.3 cm^3 of water, 1.72 g of DL-dithiothreitol and 772 mg of 2-amino-1,3-benzothiazol-6-yl thiocyanate after 24 hours at 80°C. 1.04 g of 6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.49 - 1.76 (m, 6 H) 1.83 - 1.97 (m, 2 H) 5.12 - 5.22 (m, 1 H) 6.99 (d, *J*=9.8 Hz, 1 H) 7.28 (d, *J*=8.6 Hz, 1 H) 7.34 (dd, *J*=8.3, 2.0 Hz, 1 H) 7.61 (s, 2H) 7.90 (d, *J*=2.0 Hz, 1 H) 8.23 (d, *J*=9.8 Hz, 1 H)

MASS SPECTRUM: UPLC-SQD: MH+ m/z=385+

b) 3-Chloro-6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazine may be prepared in a manner similar to that of Example **1c**, but starting with 914 mg of cyclopentanol in 20 cm^3 of tetrahydrofuran, 254mg of sodium hydride at 60% in oil and 1 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine (commercial), after reaction for 6 hours 30 minutes. 896 mg of 3-chloro-6-

(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazine are thus obtained in the form of a colourless oil that crystallizes, the characteristics of which are as follows:
MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=239+

Example 12:

N-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide

N-(6-{[6-(Cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide may be prepared in a manner similar to that of Example **1a**, but starting with 300 mg of 6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine **(11a)** in 5 cm^3 of pyridine with 0.140 cm^3 of cyclopropanecarboxylic acid chloride, after 3 hours of reaction at 20°C. 277 mg of N-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide are thus obtained in the form of a white powder, the characteristics of which are as follows:
1H NMR SPECTRUM (400 MHz, DMSO-*d*6) δ ppm 0.84 - 1.00 (m, 4 H) 1.44 - 1.71 (m, 6 H) 1.73 - 1.88 (m, 2 H) 1.92 - 2.04 (m, 1 H) 5.04 - 5.17 (m, 1 H) 7.01 (d, *J*=9.8 Hz, 1 H) 7.46 (dd, *J*=8.4, 1.8 Hz, 1 H) 7.67 (d, *J*=8.6 Hz, 1 H) 8.13 (d, *J*=2.0 Hz, 1 H) 8.26 (d, *J*=9.8 Hz, 1 H) 12.67 (br. s, 1 H)
MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=453+; MH- =451-

Example 13:

N-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide

N-(6-{[6-(Cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide may be prepared in a manner similar to that of Example **1a**, but starting with 250 mg of 6-{[6-(cyclopentyloxy)[1,2,4]triazolo-[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine **11a** in 5 cm^3 of pyridine with 2.5 cm^3 of acetic anhydride after reaction for 48 hours at 20°C. 255 mg of N-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-

sulfanyl}-1,3-benzothiazol-2-yl)acetamide are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.44 - 1.71 (m, 6 H) 1.71 - 1.88 (m, 2 H) 2.19 (s, 3 H) 5.04 - 5.15 (m, 1 H) 7.01 (d, *J*=9.8 Hz, 1 H) 7.46 (dd, *J*=8.6, 2.0 Hz, 1 H) 7.67 (d, *J*=8.6 Hz, 1 H) 8.14 (d, *J*=2.0 Hz, 1 H) 8.26 (d, *J*=9.8 Hz, 1 H) 12.37 (s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=427+; MH- =425-

Example 14:

1-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea

a) 1-(6-{[6-(Cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea may be prepared in a manner similar to that of Example **5a**, but starting with 778 mg of a mixture of phenyl (6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate and diphenyl (6-{[6-(cyclopentyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)imidodicarbonate in 10 cm^3 of tetrahydrofuran, 0.32 cm^3 of 2-(morpholin-1-yl)ethanamine and 1.04 cm^3 of triethylamine at 20°C. 127 mg of 1-(6-{[6-(cyclopentyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (500 MHz, DMSO-*d*6) **δ** ppm 1.48 - 1.71 (m, 6 H) 1.78 - 1.92 (m, 2 H) 2.32 - 2.46 (m, 6 H) 3.27 (q, *J*=5.9 Hz, 2 H) 3.54 - 3.64 (m, 4 H) 5.09 - 5.17 (m, 1 H) 6.80 (br. s, 1 H) 7.01 (d, *J*=9.6 Hz, 1 H) 7.41 (dd, *J*=8.5, 1.6 Hz, 1 H) 7.55 (d, *J*=8.5 Hz, 1 H) 8.08 (d, *J*=1.6 Hz, 1 H) 8.26 (d, *J*=9.6 Hz, 1 H)

10.93 (br. s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=541+; MH- =539-

b) The mixture of phenyl (6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyrid-azin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate and diphenyl (6-{[6-

(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)imidodicarbonate may be prepared in a manner similar to that of Example **4a**, but starting with 326 mg of 6-{[6-(cyclopentyloxy)[1,2,4]triazolo-[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine **(11a)** and 0.21 cm^3 of phenyl chlorocarbonate in 5 cm^3 of pyridine. 892 mg of a beige-coloured powder of a mixture of phenyl (6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate and diphenyl (6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)imidodicarbonate are thus obtained, which product is used without further purification in the following step:

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=505+; MH- = 503-

Example 15:

1-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea

a) 1-(6-{[6-(Cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea may be prepared in a manner similar to that of Example **1b**, but starting with 305 mg of 1-[2-(morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea **(2b)**, 5 cm^3 of degassed ethanol, 4 mg of potassium dihydrogen phosphate in 0.1 cm^3 of water, 347 mg of DL-dithiothreitol and 202 mg of 3-chloro-6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazine. 253 mg of 1-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.24 - 1.40 (m, 2 H) 1.42 - 1.58 (m, 6 H) 1.58 - 1.70 (m, 2 H) 1.78 - 1.93 (m, 2 H) 2.36 - 2.45 (m, 6 H) 3.22 - 3.28 (m, 2 H) 3.59 (t, *J*=4.4 Hz, 4 H) 4.81 - 4.91 (m, 1 H) 6.77 (br. s, 1 H) 7.01 (d, *J*=10.0 Hz, 1 H) 7.36 (dd, *J*=8.6, 2.0 Hz, 1 H) 7.55 (d, *J*=8.6 Hz, 1 H) 8.00 (d, *J*=1.7 Hz, 1 H) 8.26 (d, *J*=9.8 Hz, 1 H) 10.87 (br. s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=569+; MH- =567-

b) 3-Chloro-6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazine may be prepared in a manner similar to that of Example **1c**, but starting with 1.21 g of cycloheptanol in 15 cm^3 of tetrahydrofuran, 254 mg of sodium hydride at 60% in oil and 1 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine (commercial). 453 mg of 3-chloro-6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazine are thus obtained in the form of a colourless oil that crystallizes, the characteristics of which are as follows:

MASS SPECTRUM: Waters ZQ: MH+ m/z=267+

Example 16:

6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine

6-{[6-(Cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine may be prepared in a manner similar to that of Example **1b**, but starting with 249 mg of 3-chloro-6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazine **(15b)** in 5 cm^3 of degassed ethanol, 5 mg of potassium dihydrogen phosphate in 0.1 cm^3 of water, 432 mg of DL-dithiothreitol and 193 mg of 2-amino-1,3-benzothiazol-6-yl thiocyanate after 24 hours at 80°C. 260 mg of 6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.29 - 1.74 (m, 10 H) 1.86 - 1.97 (m, 2 H) 4.87 - 4.99 (m, 1 H) 7.00 (d, *J*=9.8 Hz, 1 H) 7.23 - 7.31 (m, 2 H) 7.60 (s, 2 H) 7.80 - 7.85 (m, 1 H) 8.24 (d, *J*=9.8 Hz, 1 H)

MASS SPECTRUM: Waters ZQ: MH+ m/z=413+; MH- =411-

Example 17:

N-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide

N-(6-{[6-(Cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide may be prepared in a manner similar to that of

Example **1a**, but starting with 85 mg of 6-{[6-(cycloheptyloxy)[1,2,4]triazolo-[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine **(16a)** in 5 cm^3 of pyridine with 0.160 cm^3 of acetic anhydride after reaction for 24 hours at 20°C. 90 mg of N-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)acetamide are thus obtained in the form of a yellow powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.20 - 1.35 (m, 2 H) 1.40 - 1.55 (m, 6 H) 1.54 - 1.66 (m, 2 H) 1.76 - 1.89 (m, 2 H) 2.19 (s, 3 H) 4.78 - 4.88 (m, 1 H) 7.01 (d, *J*=9.8 Hz, 1 H) 7.40 (dd, *J*=8.6, 2.0 Hz, 1 H) 7.67 (d, *J*=8.6 Hz, 1 H) 8.06 (d, *J*=2.0 Hz, 1 H) 8.27 (d, *J*=9.8 Hz, 1 H) 12.38 (br. s, 1 H)

MASS SPECTRUM: Waters ZQ: MH+ m/z=455+; MH- =453-

Example 18:

N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide

a) N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide may be prepared in a manner similar to that of Example **1a**, but starting with 150 mg of 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclohexyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine in 1 cm^3 of pyridine with 0.5 cm^3 of acetic anhydride after reaction for 18 hours at 20°C. 65 mg of N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)acetamide are thus obtained in the form of a pale beige powder, the characteristics of which are as follows:

1H NMR SPECTRUM (300 MHz, DMSO-*d*6) **δ** ppm 0.95 - 1.32 (m, 5 H) 1.45 - 1.67 (m, 3 H) 1.68 - 1.84 (m, 2 H) 2.19 (s, 3 H) 3.35 - 3.45 (m, 1 H) 6.79 (d, *J*=10.0 Hz, 1 H) 7.25 (d, *J*=7.0 Hz, 1 H) 7.38 (dd, *J*=8.5, 2.0 Hz, 1 H) 7.64 (d, *J*=8.5 Hz, 1 H) 7.92 (d, *J*=10.0 Hz, 1 H) 8.05 (d, *J*=2.0 Hz, 1 H) 12.35 (br. s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=440+; MH- =438-

b) 3-[(2-Amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclohexyl[1,2,4]triazolo-[4,3-b]pyridazin-6-amine may be prepared in a manner similar to that of Example **1b**, but starting with 607 mg of 3-chloro-N-cyclohexyl[1,2,4]triazolo-[4,3-b]pyridazin-6-amine in 10 cm^3 of degassed ethanol, 12 mg of potassium dihydrogen phosphate in 1 cm^3 of water, 1.12 g of DL-dithiothreitol and 500 mg of 2-amino-1,3-benzothiazol-6-yl thiocyanate after 24 hours at 80°C. 768 mg of 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclohexyl[1,2,4]-triazolo[4,3-b]pyridazin-6-amine are thus obtained in the form of a white powder, the characteristics of which are as follows:

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=398+; MH- =396-

c) 3-Chloro-N-cyclohexyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine may be prepared in the following manner:

2.3 cm^3 of cyclohexylamine and 3.7 cm^3 of triethylamine are added to a solution of 5 g of commercial 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine in 50 cm^3 of N,N-dimethylformamide. The reaction is stirred at 20°C for 18 hours. A further 1.1 cm^3 of cyclohexylamine and 7.5 cm^3 of triethylamine are then added and the reaction is stirred at 50°C for 4 hours. The reaction mixture is cooled to 20°C, followed by addition of 60 cm^3 of water. The white precipitate is filtered off by suction, and then washed successively with water and ether. 3 g of 3-chloro-N-cyclohexyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine are thus obtained in the form of a white powder. After leaving overnight, the precipitate formed in the first filtrate, obtained above, is filtered off by suction and washed successively with N,N-dimethylformamide, with demineralized water and with methanol. A second crop of 1.42 g of 3-chloro-N-cyclo-hexyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine is thus obtained in the form of a yellow powder, the characteristics of which are as follows:

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=252+; MH- =250-

Example 19:

1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea

a) 1-(6-{[6-(Cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea may be prepared in a manner similar to that of Example **1b**, but starting with 300 mg of 2-{[(2-pyrrolidinylethyl)carbamoyl]amino}-1,3-benzothiazol-6-yl thiocyanate in 6 cm^3 of degassed ethanol, 4 mg of potassium dihydrogen phosphate in 0.6 cm^3 of water, 400 mg of DL-dithiothreitol and 240 mg of 3-chloro-N-cyclohexyl[1,2,4]-triazolo[4,3-b]pyridazin-6-amine **(18c)** after 18 hours at 80°C. 193 mg of 1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea are thus obtained in the form of a pale yellow powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.00 - 1.34 (m, 6 H) 1.46 - 1.74 (m, 6 H) 1.75 - 1.86 (m, 2 H) 2.40 - 2.57 masked (m, 6 H) 3.21 - 3.28 (m, 2 H) 3.39 - 3.49 (m, 1 H) 6.79 (d, *J*=10.0 Hz, 1 H) 6.81 - 6.88 (m, 1 H) 7.25 (d, *J*=7.0 Hz, 1 H) 7.35 (dd, *J*=8.5, 2.0 Hz, 1 H) 7.52 (d, *J*=8.5 Hz, 1 H) 7.90 (d, *J*=10.0 Hz, 1 H) 7.98 (d, *J*=2.0 Hz, 1 H) 10.81 (br. s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=538+; MH- =536-

b) 2-{[(2-Pyrrolidinylethyl)carbamoyl]amino}-1,3-benzothiazol-6-yl thiocyanate may be prepared in the following manner:

1.4 cm^3 of 2-pyrrolidinylethanamine are added to a solution of 3 g of phenyl (6-thiocyanato-1,3-benzothiazol-2-yl)carbamate in 90 cm^3 of tetrahydrofuran at 20°C. After 24 hours, the reaction mixture is concentrated to dryness under reduced pressure. Ethyl ether is added to the oily yellow residue obtained. The precipitate formed is filtered off by suction. 3.33 g of 2-{[(2-pyrrolidinylethyl)carbamoyl]amino}-1,3-benzothiazol-6-yl thiocyanate are thus obtained in the form of a yellowish powder, the characteristics of which are as follows:

MASS SPECTRUM: Waters ZQ: MH+ m/z=348+; MH- =346-

c) Phenyl (6-thiocyanato-1,3-benzothiazol-2-yl)carbamate was prepared in the following manner:

7.5 g of phenyl chlorocarbonate and then 4.05 g of sodium hydrogen carbonate and 9.4 cm^3 of water are added to a solution of 2.5 g of commercial 2-amino-1,3-benzothiazol-6-yl thiocyanate in 94 cm^3 of tetrahydrofuran, at 20°C. The resulting mixture is then stirred at 20°C for 20 hours and then extracted with 2x150 cm^3 of ethyl acetate. The organic phases are combined and then washed with 3X50 cm^3 of saturated aqueous sodium hydrogen carbonate solution. The organic phase obtained is dried over magnesium sulfate and then concentrated to dryness under reduced pressure. The residue is taken up in 50 cm^3 of water and then filtered off by suction and dried under vacuum at 20°C. 3.45 g of phenyl (6-thiocyanato-1,3-benzothiazol-2-yl)carbamate are thus obtained in the form of a pale yellow solid, the characteristics of which are as follows:

MASS SPECTRUM: LC-MS-DAD-ELSD: MH+ m/z =328+; MH- = 326-

Example 20:

trans-4-{[3-({2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}-sulfanyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]amino}cyclohexyl cyclopropanecarboxylate

a) trans-4-{[3-({2-[(Cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}-sulfanyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]amino}cyclohexyl cyclopropanecarboxylate may be prepared in a manner similar to that of Example **1a**, but starting with 300 mg of trans-4-({3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl][1,2,4]triazolo[4,3-b]pyridazin-6-yl}amino)cyclohexanol in 2.1 cm^3 of pyridine with 0.133 cm^3 of cyclopropanecarboxylic acid chloride after reaction for 18 hours at 20°C. 303 mg of trans-4-{[3-({2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}sulfanyl)[1,2,4]triazolo[4,3-b]-pyridazin-6-yl]amino}cyclohexyl cyclopropanecarboxylate are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 0.76 - 1.01 (m, 8 H) 1.06 - 1.32 (m, 4 H) 1.51 - 1.65 (m, 1 H) 1.67 - 1.81 (m, 4 H) 1.93 - 2.05 (m, 1 H) 3.30 - 3.38 (m, 1 H) 4.44 - 4.61 (m, 1 H) 6.78 (d, *J*=9.8 Hz, 1 H) 7.20 - 7.34 (m, 2 H) 7.62 (d, *J*=8.6 Hz, 1 H) 7.93 (d, *J*=9.8 Hz, 1 H) 8.05 (d, *J*=2.0 Hz, 1 H) 12.64 (br. s,1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=550+; MH- =548-

b) trans-4-({3-[(2-Amino-1,3-benzothiazol-6-yl)sulfanyl][1,2,4]triazolo[4,3-b]pyridazin-6-yl}amino)cyclohexanol may be prepared in a manner similar to that of Example **1b**, but starting with 1 g of 2-amino-1,3-benzothiazol-6-yl thiocyanate in 20 cm^3 of degassed ethanol, 23 mg of potassium dihydrogen phosphate in 2 cm^3 of water, 2.32 g of DL-dithiothreitol and 1.29 g of trans-4-[(3-chloro[1,2,4]triazolo[4,3-b]pyridazin-6-yl)amino]cyclohexanol after 18 hours at 80°C. 1.8 g of trans-4-({3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl][1,2,4]triazolo[4,3-b]pyridazin-6-yl}amino)cyclohexanol are thus obtained in the form of a cream-white powder, the characteristics of which are as follows:

MASS SPECTRUM: Waters ZQ: MH+ m/z=414+; MH- =412-

c) trans-4-[(3-Chloro[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-amino]cyclohexanol may be prepared in a manner similar to that of Example **18c**, but starting with 5 g of commercial 3,6-dichloro[1,2,4]triazolo-[4,3-b]pyridazine in 50 cm^3 of N,N-dimethylformamide, 6 g of trans-4-aminocyclohexanol hydrochloride and 17 cm^3 of triethylamine after 48 hours at 20°C and 4 hours at 50°C. 3.5 g of trans-4-[(3-chloro[1,2,4]triazolo[4,3-b]-pyridazin-6-yl)amino]cyclohexanol are thus obtained in the form of a white powder, the characteristics of which are as follows:

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=268+; MH- =266-

Example 21:

N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide

N-(6-{[6-(Cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide may be prepared in a manner similar to that of Example **1a**, but starting with 300 mg of 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclohexyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine **(18b)** in 2.1 cm^3 of pyridine with 0.14 cm^3 of cyclopropanecarboxylic acid chloride, after reaction for 18 hours at 20°C. 268 mg of N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-cyclopropanecarboxamide are thus obtained in the form of a cream-white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 0.86 - 1.00 (m, 4 H) 1.01 - 1.28 (m, 5 H) 1.48 - 1.66 (m, 3 H) 1.70 - 1.83 (m, 2 H) 1.92 - 2.04 (m, 1 H) 3.36 - 3.45 (m, 1 H) 6.79 (d, *J*=9.8 Hz, 1 H) 7.25 (d, *J*=7.1 Hz, 1 H) 7.39 (d, *J*=8.6 Hz, 1 H) 7.65 (d, *J*=8.3 Hz, 1 H) 7.91 (d, *J*=9.8 Hz, 1 H) 8.03 (s, 1 H) 12.65 (br. s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=466+; MH- =464-

Example 22:

N-[6-({6-[(trans-4-hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]acetamide

a) N-[6-({6-[(trans-4-Hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]acetamide may be prepared in the following manner:

0.08 cm^3 of acetyl chloride and 0.16 cm^3 of triethylamine are added to a solution of 114 mg of trans-4-({3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-[1,2,4]triazolo[4,3-b]pyridazin-6-yl}amino)cyclohexanol **(20b)** in 2 cm^3 of dichloromethane. After 18 hours, the reaction medium is concentrated to dryness under reduced pressure. The residue is taken up in water. The yellow-white precipitate formed is filtered off by suction and washed with

water and is then purified by dry deposition on Biotage Quad 25M (KP-SIL, 60 Å; 32-63 µM), eluting with a gradient of 95/5 to 70/30 of dichloromethane/(dichloromethane: 38/methanol: 17/aqueous ammonia: 2). 46 mg of N-[6-({6-[(trans-4-hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]-pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]acetamide are thus obtained in the form of a beige-coloured powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d6*) **δ** ppm 1.01 - 1.27 (m, 4 H) 1.68 - 1.86 (m, 4 H) 2.19 (s, 3 H) 3.35 - 3.44 (m, 2 H) 4.51 (d, *J*=4.6 Hz, 1 H) 6.77 (d, *J*=9.8 Hz, 1 H) 7.25 (d, *J*=6.8 Hz, 1 H) 7.42 (dd, *J*=8.4, 1.8 Hz, 1 H) 7.65 (d, *J*=8.3 Hz, 1 H) 7.92 (d, *J*=9.8 Hz, 1 H) 8.01 (d, *J*=1.7 Hz, 1 H) 12.34 (br. s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=456+; MH- =454-

Example 23:

N-[6-({6-[(trans-4-hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide

N-[6-({6-[(trans-4-Hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide may be prepared in a manner similar to that of Example **1a**, but starting with 300 mg of trans-4-({3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl][1,2,4]triazolo[4,3-b]pyridazin-6-yl}amino)cyclohexanol (**20b**) in 3 cm^3 of pyridine with 0.235 cm^3 of cyclopropanecarboxylic acid chloride, after reaction for 16 hours at 20°C. 51 mg of N-[6-({6-[(trans-4-hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide are thus obtained in the form of a beige-coloured powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d6*) **δ** ppm 0.89 - 0.99 (m, 4 H) 1.02 - 1.27 (m, 4 H) 1.68 - 1.87 (m, 4 H) 1.92 - 2.03 (m, 1 H) 3.31 - 3.45 (m, 2 H) 4.51 (d, *J*=4.4 Hz, 1 H) 6.77 (d, *J*=9.8 Hz, 1 H) 7.25 (d, *J*=7.1 Hz, 1 H) 7.43

(dd, *J*=8.6, 2.0 Hz, 1 H) 7.65 (d, *J*=8.6 Hz, 1 H) 7.91 (d, *J*=9.8 Hz, 1 H) 8.00 (d, *J*=1.7 Hz,1 H) 12.64 (br. s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=482+; MH- =480-

Example 24:

3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclopropyl[1,2,4]triazolo-[4,3-b]pyridazin-6-amine

a) 3-[(2-Amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclopropyl[1,2,4]-triazolo[4,3-b]pyridazin-6-amine may be prepared in a manner similar to that of Example **1b**, but starting with 1.4 g of 2-amino-1,3-benzothiazol-6-yl thiocyanate in 41 cm^3 of degassed ethanol, 32 mg of potassium dihydrogen phosphate in 4 cm^3 of water, 3.13 g of DL-dithiothreitol and 1.42 g of 3-chloro-N-cyclopropyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine after 18 hours at 80°C. 1.22 g of 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclopropyl[1,2,4]-triazolo[4,3-b]pyridazin-6-amine are thus obtained in the form of a cream-white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 0.41 - 0.48 (m, 2 H) 0.71 - 0.79 (m, 2 H) 2.56 - 2.65 (m, 1 H) 6.76 (d, *J*=9.8 Hz, 1 H) 7.27 (d, *J*=8.3 Hz, 1 H) 7.42 (dd, *J*=8.3, 2.0 Hz, 1 H) 7.67 (br. s, 3 H) 7.92 (d, *J*=9.8 Hz, 1 H) 7.95 (d, *J*=1.7 Hz, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=356+; MH- =354-

b) 3-Chloro-N-cyclopropyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine

DPN1.150 may be prepared in a manner similar to that of Example **18c**, but starting with 2 g of commercial 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine in 20 cm^3 of N,N-dimethylformamide, 1.1 cm^3 of cyclopropylamine and 3 cm^3 of triethylamine, after 18 hours at 20°C and 3 hours at 50°C. 1.53 g of 3-chloro-N-cyclopropyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine are thus obtained in the form of a white powder, the characteristics of which are as follows:

MASS SPECTRUM: Waters ZQ: MH+ m/z=210+; MH- =208-

Example 25:

N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide

a) N-(6-{[6-(Cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)acetamide may be prepared in a manner similar to that of Example **1a**, but starting with 300 mg of 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclopropyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine **(24a)** in 2.1 cm^3 of pyridine with 1.04 cm^3 of acetic anhydride after reaction for 18 hours at 20°C. 100 mg of N-(6-{[6-(cyclopropylamino)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 0.34 - 0.45 (m, 2 H) 0.61 - 0.74 (m, 2 H) 2.19 (s, 3 H) 2.53 - 2.58 (m, 1 H) 6.77 (d, *J*=9.5 Hz, 1 H) 7.53 (d, *J*=8.3 Hz, 1 H) 7.62 - 7.73 (m, 2 H) 7.94 (d, *J*=9.8 Hz, 1 H) 8.19 (s, 1 H) 12.38 (br. s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=398+; MH- =396-

Example 26:

N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide

a) N-(6-{[6-(Cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide may be prepared in a manner similar to that of Example **1a**, but starting with 300 mg of 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclopropyl[1,2,4]triazolo[4,3-b]pyrid-azin-6-amine **(24a)** in 3 cm^3 of pyridine with 0,16 cm^3 of cyclopropane-carboxylic acid chloride, after reaction for 18 hours at 20°C. 208 mg of N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzo-thiazol-2-yl)cyclopropanecarboxamide are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 0.34 - 0.44 (m, 2 H) 0.62 - 0.73 (m, 2 H) 0.89 - 1.01 (m, 4 H) 1.93 - 2.03 (m, 1 H) 2.52 - 2.61 (m, 1 H) 6.77 (d, *J*=9.8 Hz, 1 H) 7.53 (dd, *J*=8.6, 1.7 Hz, 1 H) 7.61 - 7.71 (m, 2 H) 7.94 (d, *J*=9.8 Hz, 1 H) 8.19 (d, *J*=1.5 Hz, 1 H) 12.66 (br. s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=424+; MH- =422-

Example 27:

1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea

a) 1-(6-{[6-(Cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea may be prepared in a manner similar to that of Example **1b**, but starting with 300 mg of 1-[2-(morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea **(2b)**, 7.5 cm^3 of degassed ethanol, 6 mg of potassium dihydrogen phosphate in 0.7 cm^3 of water, 552 mg of DL-dithiothreitol and 403 mg of 3-chloro-N-cyclohexyl[1,2,4]-triazolo[4,3-b]pyridazin-6-amine **(18c)**. 370 mg of 1-(6-{[6-(cyclohexylamino)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea are thus obtained in the form of a white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 1.08 - 1.30 (m, 5 H) 1.47 - 1.70 (m, 3 H) 1.71 - 1.89 (m, 2 H) 2.32 - 2.46 (m, 6 H) 3.22 - 3.28 (masked m, 2 H) 3.36 - 3.52 (m, 1 H) 3.59 (t, *J*=4.3 Hz, 4 H) 6.69 - 6.93 (m, 2 H) 7.25 (d, *J*=7.1 Hz, 1 H) 7.35 (dd, *J*=8.3, 2.0 Hz, 1 H) 7.52 (d, *J*=8.3 Hz, 1 H) 7.90 (d, *J*=10.0 Hz, 1 H) 7.98 (d, *J*=1.7 Hz, 1 H) 10.90 (br. s, 1 H)

MASS SPECTRUM: Waters ZQ: MH+ m/z=554+; MH- =552-

Example 28:

N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide

a) N-(6-{[6-(Cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide may be prepared in a

manner similar to that of Example **1a**, but starting with 220 mg of 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclopropyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine **(24a)** in 7 cm^3 of pyridine with 0.2 cm^3 of 3-methoxypropanoyl chloride, after reaction for 18 hours at 20°C. 81 mg of N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide are thus obtained in the form of a pale beige powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-*d*6) **δ** ppm 0.33 - 0.43 (m, 2 H) 0.62 - 0.73 (m, 2 H) 2.53 - 2.59 (m, 1 H) 2.73 (t, *J*=6.1 Hz, 2 H) 3.24 (s, 3 H) 3.64 (t, *J*=6.0 Hz, 2 H) 6.77 (d, *J*=9.5 Hz, 1 H) 7.53 (dd, *J*=8.4, 1.6 Hz, 1 H) 7.68 (d, *J*=8.6 Hz, 1 H) 7.72 (d, *J*=2.7 Hz, 1 H) 7.96 (d, *J*=9.8 Hz, 1 H) 8.22 (d, *J*=1.5 Hz, 1 H) 12.46 (br. s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=442+

Example 29:

1-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea

a) 1-(6-{[6-(Cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea may be prepared in a manner similar to that of Example **1b**, but starting with 300 mg of 1-[2-(morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea **(2b)**, 12 cm^3 of degassed ethanol, 5 mg of potassium dihydrogen phosphate in 1.2 cm^3 of water, 410 mg of DL-dithiothreitol and 187 mg of 3-chloro-N-cyclopropyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine **(24b)**, after 18 hours at 80°C. 133 mg of 1-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea are thus obtained in the form of a cream-white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-d_6 CD_3COOD) **δ** ppm 0.36 - 0.49 (m, 2 H) 0.65 - 0.82 (m, 2 H) 2.57 - 2.65 (m, 1 H) 2.96 - 3.16 (m, 6 H) 3.50 (t,

J=5.7 Hz, 4H) 3.79 (br. s, 2 H) 6.79 (d, *J*=9.8 Hz, 1 H) 6.90 - 7.05 (m, 1 H) 7.48 - 7.63 (m, 2 H) 7.66 (br. s, 1 H) 7.91 (d, *J*=9.8 Hz, 1 H) 8.16 (s, 1 H)
MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=512+; MH- =510-

Example 30:

N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²,N²-dimethylglycinamide

a) N-(6-{[6-(Cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)-N²,N²-dimethylglycinamide may be prepared in a manner similar to that of Example **1a**, but starting with 220 mg of 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclopropyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine **(24a)** in 8 cm^3 of dichloromethane with 197 mg of N,N-dimethylglycyl chloride hydrochloride and 0.26 cm^3 of triethylamine, after reaction for 18 hours at 20°C. 167 mg of N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²,N²-dimethylglycinamide are thus obtained in the form of a pale beige powder, the characteristics of which are as follows:
1H NMR SPECTRUM (500 MHz, DMSO-*d*6) **δ** ppm 0.39 (br. s, 2 H) 0.69 (d, *J*=5.2 Hz, 2 H) 2.29 (s, 6 H) 2.52 - 2.59 (m, 1 H) 3.10 - 3.25 (masked m, 2 H) 6.77 (d, *J*=9.6 Hz, 1 H) 7.53 (d, *J*=8.2 Hz, 1 H) 7.61 - 7.74 (m, 2 H) 7.95 (d, *J*=9.6 Hz, 1 H) 8.20 (s, 1 H) 12.06 (br. s, 1 H)
MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=441+; MH- =439-

Example 31:

3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclohexyl-7,8-dihydro[1,2,4]triazolo[4,3-b]pyridazin-6-amine

a) 3-[(2-Amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclohexyl-7,8-dihydro[1,2,4]triazolo[4,3-b]pyridazin-6-amine may be prepared in a manner similar to that of Example **1b**, but starting with 250 mg of 2-amino-1,3-benzothiazol-6-yl thiocyanate, 8 cm^3 of degassed ethanol, 6 mg of potassium dihydrogen phosphate in 0.8 cm^3 of water, 660 mg of DL-dithiothreitol and

306 mg of 3-chloro-N-cyclohexyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine. 202 mg of 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclohexyl-7,8-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-6-amine are thus obtained in the form of a cream-white powder, the characteristics of which are as follows:

1H NMR SPECTRUM (400 MHz, DMSO-d6) **δ** ppm 1.00 - 1.35 (m, 5 H) 1.48 - 1.74 (m, 3 H) 1.78 - 1.90 (m, 2 H) 2.56 (t, J=7.7 Hz, 2 H) 2.96 (t, J=7.7 Hz, 2 H) 3.45 - 3.55 (m, 1 H) 7.08 (d, J=7.6 Hz, 1 H) 7.16 - 7.37 (m, 2 H) 7.66 (br. s, 2 H) 7.81 (s, 1 H)

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=400+; MH- =398-

b) 3-Chloro-N-cyclohexyl-7,8-dihydro[1,2,4]triazolo[4,3-b]pyridazin-6-amine may be prepared in the following manner:

1.3 g of zinc powder are added to 500 mg of 3-chloro-N-cyclohexyl[1,2,4]-triazolo[4,3-b]pyridazin-6-amine (18c) in 16 cm^3 of glacial acetic acid at 20°C. After stirring for 2 hours, the suspension is filtered through filter paper and the filtrate is concentrated to dryness under reduced pressure. The solid residue obtained is purified by chromatography on silica, by dry deposition on a Biotage Quad 12/25 cartridge (KP-SIL, 60 Å; 32-63 µM), eluting with a 95/5 to 90/10 gradient of dichloromethane/methanol. 317 mg of 3-chloro-N-cyclohexyl-7,8-dihydro[1,2,4]triazolo[4,3-b]pyridazin-6-amine are thus obtained in the form of a white powder, the characteristics of which are as follows:

MASS SPECTRUM: Waters UPLC-SQD: MH+ m/z=254+; MH- =252-

Example 32:

ethyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate

a) Ethyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate may be prepared in the following manner:

320 mg of 2-[(morpholin-4-ylcarbonyl)amino]-1,3-benzothiazol-6-yl thiocyanate (**32b**) in 7 cm^3 of ethanol are placed in a 10 cm^3 microwave vial equipped with a stirrer, at 20°C. A stream of argon is bubbled through the mixture for 5 minutes, followed by adding 408 mg of potassium dihydrogen

phosphate in 0.25 cm^3 of water, 463 mg of DL-dithiothreitol and 252 mg of 3-chloro-6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazine (**1c**). The mixture is stirred in a microwave oven for 1 hour at 120°C. The reaction mixture is then concentrated to dryness under vacuum and the solid residue is then purified by two successive chromatographies on a Merck silica cartridge by solid deposition, eluting with a 99/1 to 97/3 gradient of dichloromethane/methanol. 77 mg of ethyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)carbamate are thus obtained in the form of a white solid, the characteristics of which are as follows:

MASS SPECTRUM: LC/MS Electrospray on WATERS UPLC - SQD:

Retention time Rt (min) = 1.06; [M+H]+: m/z 471; [M-H]-: m/z 469

1H NMR Spectrum (400 MHz, **δ** in ppm, DMSO-d6): 1.15 to 1.40 (m, 8 H); 1.42 to 1.64 (m, 3 H); 1.79 (d, *J*=13.2 Hz, 2 H); 4.24 (q, *J*=7.1 Hz, 2 H); 4.67 (m, 1 H); 7.02 (d, *J*=9.8 Hz, 1 H); 7.39 (dd, *J*=1.8 and 8.2 Hz, 1 H); 7.62 (d, *J*=8.6 Hz, 1 H); 8.05 (s, 1 H); 8.28 (d, *J*=9.8 Hz, 1 H); 12.06 (broad s, 1 H)

b) 2-[(Morpholin-4-ylcarbonyl)amino]-1,3-benzothiazol-6-yl thiocyanate may be prepared in a manner similar to that of Example **2c**, but starting with 2.29 g of phenyl (6-thiocyanato-1,3-benzothiazol-2-yl)carbamate **(2d)** in a mixture of 70 cm^3 of tetrahydrofuran and 0.602 cm^3 of morpholine at 50°C for 26 hours. 2.12 g of 2-[(morpholin-4-ylcarbonyl)amino]-1,3-benzothiazol-6-yl thiocyanate are thus obtained in the form of a white solid, the characteristics of which are as follows:

MASS SPECTRUM: Waters UPLC-SQD:

Retention time Rt (min) = 0.73; [M+H]+: m/z 321; [M-H]-: m/z 319

Example 33:

2-chloro-N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)acetamide

a) 2-Chloro-N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)acetamide may be prepared in the following manner:

0.1 cm^3 of chloroacetyl chloride is added dropwise to 200 mg of 6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**1b**) in 2 cm^3 of dichloromethane and 0.5 cm^3 of pyridine at 0-5°C. The resulting solution is stirred for 30 minutes at 20°C, and the medium is then evaporated to dryness under argon at 20°C. The residue is purified by chromatography on a Merck silica cartridge by solid deposition, eluting with a gradient of from 100% dichloromethane to 92/8 dichloromethane/(dichloromethane: 38/methanol: 17/aqueous ammonia: 2). After slurrying in ether and drying under vacuum, 102 mg of 2-chloro-N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide are obtained in the form of a white solid, the characteristics of which are as follows:

MASS SPECTRUM: Waters UPLC-SQD:

Retention time Rt (min) = 1.03; [M+H]+: m/z 475; [M-H]-: m/z 473

1H NMR Spectrum (400 MHz, **δ** in ppm, DMSO-d6): 1.10 to 1.38 (m, 5 H); 1.41 to 1.65 (m, 3 H); 1.77 (m, *J*=12.2 Hz, 2 H); 4.44 (s, 2 H); 4.66 (m, 1 H); 7.03 (d, *J*=9.8 Hz, 1 H); 7.42 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.70 (d, *J*=8.6 Hz, 1 H); 8.08 (d, *J*=2.0 Hz, 1 H); 8.29 (d, *J*=10.0 Hz, 1 H); 12.75 (broad s, 1 H)

Example 34:

N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²-cyclopropylglycinamide

a) N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²-cyclopropylglycinamide may be prepared in the following manner:

0.35 cm^3 of cyclopropylamine is added to 280 mg of 2-chloro-N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-acetamide **(33)** in 4 cm^3 of pyridine at 20°C. After stirring for 5 hours, the reaction medium is evaporated to dryness at 20°C. The residue is purified by chromatography on a Merck silica cartridge by solid deposition, eluting with a gradient of from 100% de dichloromethane to 97/3

dichloromethane/methanol. 110 mg of N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo-[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2-cyclopropylglycin-amide are thus obtained in the form of a yellow solid, the characteristics of which are as follows:

MASS SPECTRUM: Waters UPLC-SQD:

Retention time Rt (min) = 0.74; [M+H]+: m/z 496; [M-H]-: m/z 494

1H NMR Spectrum (400 MHz, **δ** in ppm, DMSO-d6): 0.19 to 0.40 (m, 4 H); 1.14 to 1.26 (m, 3 H); 1.33 (m, 2 H); 1.41 to 1.66 (m, 3 H); 1.78 (m, 2 H); 2.17 (m, 1 H); 3.51 (s, 2 H); 4.60 to 4.72 (m, 1 H); 7.03 (d, *J*=9.8 Hz, 1 H); 7.41 (dd, *J*=1.5 and 8.3 Hz, 1 H); 7.68 (d, *J*=8.8 Hz, 1 H); 8.08 (s, 1 H); 8.28 (d, *J*=9.8 Hz, 1 H)

Example 35:

6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine

a) 6-{[6-(Cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine may be prepared in a manner similar to that of Example **1b**, but starting with 1.07 g of 2-amino-1,3-benzothiazol-6-yl thiocyanate, 15 cm^3 of degassed ethanol, 20 mg of potassium dihydrogen phosphate in 0.1 cm^3 of water, 1.99 g of DL-dithiothreitol and 964 mg of 3-chloro-6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazine. 1.1 g of 6-{[6-(cyclobutyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine are thus obtained in the form of a whitish powder, the characteristics of which are as follows:

MASS SPECTRUM: Waters ZQ:

Retention time Rt (min) = 3.39; [M+H]+: m/z 371; [M-H]-: m/z 369

1H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.66 (m, 1 H); 1.80 (m, 1 H); 2.01 to 2.13 (m, 2 H); 2.31 to 2.40 (m, 2 H); 4.96 (qd, *J*=7.1 and 7.3 Hz, 1 H); 7.04 (d, *J*=9.8 Hz, 1 H); 7.29 (d, *J*=8.3 Hz, 1 H); 7.34 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.62 (s, 2 H); 7.88 (d, *J*=1.7 Hz, 1 H); 8.26 (d, *J*=9.8 Hz, 1 H)

b) 3-Chloro-6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazine may be prepared in a manner similar to that of Example **1c**, but starting with 954 mg of cyclobutanol in 10 cm^3 of tetrahydrofuran, 317 mg of sodium hydride at 60% in oil and 1 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine (commercial). 1.03 g of 3-chloro-6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazine are thus obtained in the form of a beige-coloured powder, the characteristics of which are as follows:

1H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.63 to 1.96 (m, 2 H); 2.07 to 2.24 (m, 2 H); 2.41 to 2.52 (partially masked m, 2 H); 4.95 to 5.34 (m, 1 H); 7.10 (d, *J*=9.8 Hz, 1 H); 8.28 (d, *J*=9.8 Hz, 1 H)

Example 36:

N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide

a) N-(6-{[6-(Cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide may be prepared in the following manner:

A mixture of 273 mg of (4-ethylpiperazin-1-yl)acetic acid (commercial), 0.28 cm^3 of diisopropylethylamine and 411 mg of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) in 3 cm^3 of N,N-dimethylformamide at 20°C is stirred for 1 hour at 20°C. 200 mg of 6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine **(35a)** are added to the reaction medium. After 18 hours, the solution is poured into ice-water and the precipitate is filtered off. The yellow paste isolated is taken up in a 90/10 ethyl acetate/methanol mixture. The solution obtained is dried over magnesium sulfate, filtered and then concentrated to dryness under vacuum. The oily residue is purified on SPOT II by chromatography on a silica cartridge (SVF D26 Si60; 15-40 µM; 25 g), eluting with a gradient of from 96/4 dichloromethane/methanol to 100% methanol. 127 mg of N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-

1,3-benzothiazol-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide are thus obtained in the form of a yellow powder, the characteristics of which are as follows:

MASS SPECTRUM: Waters ZQ

Retention time Rt (min) = 3.10; [M+H]+: m/z 525; [M-H]-: m/z 523

1H NMR Spectrum (400 MHz, **δ** in ppm, DMSO-d_6): 1.00 (t, *J*=7.2 Hz, 3 H); 1.59 (m, 1 H); 1.73 (m, 1 H); 1.94 to 2.09 (m, 2 H); 2.20 to 2.31 (m, 2 H); 2.32 to 2.58 (partially masked m, 10 H); 3.34 (s, 2 H); 4.90 (m, 1 H); 7.06 (d, *J*=9.8 Hz, 1 H); 7.48 (dd, *J*=1.8 and 8.6 Hz, 1 H); 7.71 (d, *J*=8.6 Hz, 1 H); 8.14 (d, *J*=1.8 Hz, 1 H); 8.30 (d, *J*=9.8 Hz, 1 H); 12.12 (very broad m, 1 H)

Example 37:

N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²,N²-diethylglycinamide

a) N-(6-{[6-(Cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N²,N²-diethylglycinamide may be prepared in the following manner:

A mixture of 827 mg of sodium (diethylamino)acetate (commercial) in 5.5 cm^3 of a 2N solution of hydrogen chloride in ether is stirred for 1 hour at 20°C. The resulting suspension is evaporated to dryness under vacuum. 8 cm^3 of pyridine, 200 mg of 6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-amine **(35a)** and 1.03 g of N-(3-dimethylaminopropyl)N'-ethylcarbodiimide hydrochloride are added to the white residue obtained, at 20°C. After 5 hours, the brown reaction medium is evaporated to dryness. The residue is taken up in toluene and the mixture is again evaporated to dryness under vacuum. The residue is taken up in water and the mixture is extracted with ethyl acetate and then evaporated to dryness. The residue is purified by dry deposition on silica and chromatographed on a Biotage Quad 12/25 cartridge (KP-SIL, 60 Å; 32-63 µM), eluting with a 100/0 to 98/2 gradient of dichloromethane/methanol. 135 mg of N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-

benzothiazol-2-yl)-N²,N²-diethylglycinamide are thus obtained in the form of a beige-coloured powder, the characteristics of which are as follows:

MASS SPECTRUM: Waters UPLC-SQD:

Retention time Rt (min) = 0.72; [M+H]+: m/z 484; [M+2H]2+: m/z 242.5 (base peak); [M-H]-: m/z 482

1H NMR Spectrum (400 MHz, **δ** in ppm, DMSO-d_6): 1,00 (t, *J*=7.2 Hz, 6 H); 1.52 to 1.66 (m, 1 H); 1.68 to 1.80 (m, 1 H); 1.95 to 2.09 (m, 2 H); 2.20 to 2.31 (m, 2 H); 2.62 (q, *J*=7.2 Hz, 4 H); 3.40 (s, 2 H); 4.90 (m, 1 H); 7.06 (d, *J*=9.8 Hz, 1 H); 7.47 (dd, *J*=1.9 and 8.5 Hz, 1 H); 7.69 (d, *J*=8.5 Hz, 1 H); 8.13 (d, *J*=1.9 Hz, 1 H); 8.29 (d, *J*=9.8 Hz, 1 H); 11.54 (very broad m, 1 H)

Other examples and intermediates thereof prepared by analogy with the above examples are described in the table below:

Ex.	Name	Preparation similar to Example:	Starting with:	Amount isolated
38	N-(6-{[6-(cycloheptyl-oxy)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclo-propanecarboxamide	**1a**	86 mg of 6-{[6-(cycloheptyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**16a**) and 44 mg of cyclopropanecarboxylic acid chloride	52 mg
39	1-(6-{[6-(cyclo-hexylamino)[1,2,4]triazolo-[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)-3-[3-(morpholin-4-yl)propyl]urea	**1b**	105 mg of 3-chloro-N-cyclohexyl[1,2,4]-triazolo[4,3-b]pyridazin-6-amine (**18c**) and 155 mg of 2-({[3-(morpholin-4-yl)propyl]-carbamoyl}amino)-1,3-benzothiazol-6-yl thiocyanate (**39b**)	168 mg
39b	2-({[3-(morpholin-4-yl)propyl]carbamoyl}amino)-1,3-benzothiazol-6-yl thiocyanate	**2c**	500 mg of phenyl (6-thiocyanato-1,3-benzo-thiazol-2-yl)carbamate (**2d**) and 264 mg of N-(3-aminopropyl)morpholine (commercial)	634 mg
40	1-(6-{[6-(cyclo-hexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[3-(morpholin-4-yl)propyl]urea	**1b**	200 mg of 3-chloro-6-(cyclo-hexyloxy)[1,2,4]triazolo[4,3-b]pyridazine (**1c**) and 299 mg of 2-({[3-(morpholin-4-yl)propyl]carbamoyl}amino)-1,3-benzo-thiazol-6-yl thiocyanate (**39b**)	149 mg
41	1-(6-{[6-(cyclobutyl-oxy)[1,2,4]triazolo[4,3-b]-	**2a**	200 mg of 3-chloro-6-(cyclobutyloxy)[1,2,4]-triazolo[4,3-b]pyridazine (**35b**) and 422 mg	245 mg

	pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea		of 1-[2-(morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea (**2b**)	
42	rac-1-[2-(morpholin-4-yl)-ethyl]-3-{6-[(6-{[trans-4-(trifluoromethyl)cyclohexyl]-oxy}[1,2,4]triazolo[4,3-b]-pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}urea	**2a**	200 mg of rac-3-chloro-6-{[trans-4-(trifluoro-methyl)cyclohexyl]oxy}[1,2,4]triazolo[4,3-b]-pyridazine (**42b**) and 295 mg of 1-[2-(morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea (**2b**)	199 mg
42b	rac-3-chloro-6-{[trans-4-(trifluoromethyl)cyclo-hexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazine	**1c**	1 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyrid-azine (commercial) and 2.19 g of rac-trans-4-(trifluoromethyl)cyclohexan-1-ol (commercial)	997 mg
43	N-(6-{[6-(cyclo-hexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-cyclo-propylacetamide	**32a**	252 mg of 3-chloro-6-(cyclo-hexyloxy)[1,2,4]triazolo[4,3-b]pyridazine (**1c**) and 289 mg of 2-[(cyclopropylacetyl)-amino]-1,3-benzothiazol-6-yl thiocyanate (**43b**)	110 mg
43b	2-[(cyclopropylacetyl)amino]-1,3-benzothiazol-6-yl thiocyanate	**1a**	830 mg of 2-amino-1,3-benzothiazol-6-yl thiocyanate and 1 eq of cyclopropylacetyl chloride solution (**43c**)	383 mg
43c	cyclopropylacetyl chloride		1 g of cyclopropylacetic acid and 0.75 cm^3 of $SOCl_2$ under conditions similar to those described by Kreimeyer et al. J. Med. Chem. **1999,** 42, 4394	solution used directly
44	N-(6-{[6-(cyclobutyl-oxy)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclo-propanecarboxamide	**1a**	70 mg of 6-{[6-(cyclobutyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**35a**) and 0.037 cm^3 of cyclopropanecarboxylic acid chloride	64 mg
45	rac-cis/trans-N-{4-[(3-{[2-({[2-(morpholin-4-yl)ethyl]-carbamoyl}amino)-1,3-benzothiazol-6-yl]sulfanyl}-[1,2,4]triazolo[4,3-b]pyrid-azin-6-yl)oxy]cyclohexyl}-acetamide	**2a**	200 mg of rac-cis/trans-N-{4-[(3-chloro[1,2,4]triazolo[4,3-b]pyridazin-6-yl)oxy]cyclohexyl}acetamide (**45b**) and 306 mg of 1-[2-(morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea (**2b**)	89 mg mixture of isomers (30/70 cis/trans)
45b	rac-cis/trans-N-{4-[(3-chloro[1,2,4]triazolo[4,3-b]-pyridazin-6-yl)oxy]cyclo-hexyl}acetamide	**1c**	1 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyrid-azine (commercial) and 2.04 g of N-(4-hydroxycyclohexyl)acetamide (commercial)	2.49 g mixture of isomers (30/70 cis/trans)
46	N-{6-[(6-{[4-(trifluoromethyl)-cyclohexyl]oxy}[1,2,4]-triazolo[4,3-b]pyridazin-3-yl)-	**1a**	440 mg of 6-[(6-{[4-(trifluoromethyl)cyclo-hexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-amine (**46b**)	330 mg

	sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide		and 197 mg of cyclopropanecarbonyl chloride	
46b	6-[(6-{[4-(trifluoromethyl)-cyclohexyl]oxy}[1,2,4]-triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-amine	**1b**	323 mg of 2-amino-1,3-benzothiazol-6-yl thiocyanate and 500 mg of 3-chloro-6-{[4-(trifluoromethyl)cyclohexyl]oxy}[1,2,4]-triazolo[4,3-b]pyridazine (**42b**)	496 mg
47	1-[6-({6-[(trans-4-hydroxy-cyclohexyl)oxy][1,2,4]-triazolo[4,3-b]pyridazin-3-yl}-sulfanyl)-1,3-benzothiazol-2-yl]-3-[2-(morpholin-4-yl)-ethyl]urea	**2a**	250 mg of trans-4-[(3-chloro[1,2,4]triazolo-[4,3-b]pyridazin-6-yl)oxy]cyclohexanol (**47b**) and 378 mg of 1-[2-(morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea (**2b**)	232 mg
47b	trans-4-[(3-chloro[1,2,4]-triazolo[4,3-b]pyridazin-6-yl)oxy]cyclohexanol	**1c**	1 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyrid-azine (commercial) and 3,07 g of 1,4-cyclohexanediol (cis/trans mixture)	256 mg trans (and 214 mg cis)
48	6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine	**1b**	550 mg of 6-(bicyclo[3.1.0]hex-3-yloxy)-3-chloro[1,2,4]triazolo[4,3-b]pyridazine (**48b**) and 455 mg of 2-amino-1,3-benzothiazol-6-yl thiocyanate	574 mg
48b	6-(bicyclo[3.1.0]hex-3-yloxy)-3-chloro[1,2,4]triazolo[4,3-b]-pyridazine	**1c**	1 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyrid-azine (commercial) and 1.04 g of bicyclo[3.1.0]hexan-3-ol	968 mg
49	3-[(2-amino-1,3-benzo-thiazol-6-yl)sulfanyl]-N-cyclo-butyl[1,2,4]triazolo[4,3-b]-pyridazin-6-amine	**1b**	500 mg of 3-chloro-N-cyclobutyl[1,2,4]-triazolo[4,3-b]pyridazin-6-amine (**49b**) and 463 mg of 2-amino-1,3-benzothiazol-6-yl thiocyanate	417 mg
49b	3-chloro-N-cyclobutyl[1,2,4]-triazolo[4,3-b]pyridazin-6-amine	**18c**	2 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyrid-azine (commercial) and 1.17 cm^3 of cyclo-butylamine	2.14 g
50	N-(6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclo-butanecarboxamide	**1a**	530 mg of 6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-amine (**48**) and 0.24 cm^3 of cyclobutanecarbonyl chloride	568 mg
51	rac-6-({6-[(trans-2-fluorocyclohexyl)oxy][1,2,4]-triazolo[4,3-b]pyridazin-3-yl}-sulfanyl)-1,3-benzothiazol-2-amine	**1b**	550 mg of rac-3-chloro-6-[(trans-2-fluorocyclohexyl)oxy][1,2,4]triazolo[4,3-b]-pyridazine (**51b**) and 421 mg of 2-amino-1,3-benzothiazol-6-yl thiocyanate	249 mg
51b	rac-3-chloro-6-[(trans-2-fluorocyclohexyl)oxy][1,2,4]-triazolo[4,3-b]pyridazine	**1c**	650 mg of 3,6-dichloro[1,2,4]triazolo[4,3-b]-pyridazine and 813 mg of rac-trans-2-fluorocyclohexanol (commercial)	829 mg

52	rac-N-{6-[(6-{[(trans-2-fluorocyclohexyl]oxy}[1,2,4]-triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarbox-amide	**1a**	195 mg of rac-6-({6-[(trans-2-fluorocyclo-hexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-amine (**51**) and 0.085 cm^3 of cyclopropanecarbonyl chloride	103 mg
53	N-(6-{[6-(cyclo-butylamino)[1,2,4]triazolo-[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide	**1a**	120 mg of 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclobutyl[1,2,4]triazolo[4,3-b]pyridazin-6-amine (**49**) and 0.06 cm^3 of cyclopropanecarbonyl chloride	87 mg
54	N-(6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclo-propanecarboxamide	**1a**	110 mg of 6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-amine (**48**) and 0.051 cm^3 of cyclopropanecarbonyl chloride	112 mg
55	rac-N^2,N^2-diethyl-N-[6-({6-[(trans-2-fluorocyclo-hexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]glycin-amide	**37a**	200 mg of rac-6-({6-[(trans-2-fluorocyclo-hexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-amine (**51**) and 735 mg of sodium (diethylamino)-acetate (commercial)	164 mg
56	rac-2-(4-ethylpiperazin-1-yl)-N-{6-[(6-{[trans-2-fluorocyclohexyl]oxy}[1,2,4]-triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}acetamide	**37a**	300 mg of 6-({6-[(trans-2-fluorocyclo-hexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-amine (**51**) and 1.82 g of (4-ethylpiperazin-1-yl)acetic acid hydrobromide (commercial)	120 mg
57	rac-N-{6-[(6-{[trans-2-fluorocyclohexyl]oxy}[1,2,4]-triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-2-(morpholin-4-yl)acet-amide	**37a**	300 mg of 6-({6-[(trans-2-fluorocyclo-hexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-amine (**51**) and 1.05 g of morpholin-4-ylacetic acid (commercial)	156 mg
58	N-(6-{[6-(cyclo-butyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(morpholin-4-yl)acetamide	**37a**	200 mg of 6-{[6-(cyclobutyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**35a**) and 784 mg of morpholin-4-ylacetic acid (commercial)	96 mg
59	rac-2-(4-cyclopropyl-piperazin-1-yl)-N-{6-[(6-{[trans-2-fluorocyclo-hexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}acetamide	**37a**	200 mg of 6-({6-[(trans-2-fluorocyclo-hexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-amine (**51**) and 990 mg of potassium (4-cyclo-propylpiperazin-1-yl)acetate (**59b**)	98 mg

59b	potassium (4-cyclo-propylpiperazin-1-yl)acetate		2.1 g of bromoacetic acid and 3 g of 4-cyclopropylpiperazine.HCl under conditions similar to those described by D.T. Witiak et al.; J. Med. Chem. 1985, 28, 1228	2.66 g
60	N-(6-{[6-(cyclobutyl-oxy)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(4-cyclopropylpiperazin-1-yl)-acetamide	**37a**	150 mg of 6-{[6-(cyclobutyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**35a**) and 418 mg of potassium (4-cyclopropylpiperazin-1-yl)-acetate (**59b**)	143 mg
61	N-(6-{[6-(cyclo-butyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(1,1-dioxidothiomorpholin-4-yl)-acetamide	**37a**	150 mg of 6-{[6-(cyclobutyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**35a**) and 391 mg of (1,1-di-oxidothiomorpholin-4-yl)acetic acid (commercial)	109 mg
62	N-(6-{[6-(cyclo-butyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(1,4-oxazepan-4-yl)acetamide	**37a**	200 mg of 6-{[6-(cyclobutyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**35a**) and 489 mg of potassium 1,4-oxazepan-4-ylacetate **(62b)**	152 mg
62b	potassium 1,4-oxazepan-4-ylacetate		2.32 g of bromoacetic acid and 2.3 g of 1,4-oxazepan hydrochloride under conditions similar to those described by D.T. Witiak et al.; J. Med. Chem. 1985, 28, 1228	2.77g
63	N-(6-{[6-(cyclo-butyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide	**1a**	300 mg of 6-{[6-(cyclobutyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**35a**) and 200 mg of 3-methoxypropanoyl chloride (commercial)	101 mg
64	N-(6-{[6-(cyclobutyl-oxy)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(3,3-difluoropiperidin-1-yl)acet-amide	**37a**	200 mg of 6-{[6-(cyclobutyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine (**35a**) and 484 mg of potassium (3,3-difluoropiperidin-1-yl)-acetate (**64b**)	183 mg
64b	potassium (3,3-difluoropiperidin-1-yl)acetate		1.6 g of bromoacetic acid and 1.8 g of 3,3-difluoropiperidine under conditions similar to those described by D.T. Witiak et al.; J. Med. Chem. 1985, 28, 1228	1.16 g

The characteristics of the products of the above table are as follows:

Ex	SM	RMN
38	Retention time Tr (min) = 1.09; [M+H]+: m/z 481; [M-H]-: m/z 479	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.88 to 0.98 (m, 4 H); 1.16 to 1.35 (m, 2 H); 1.39 to 1.54 (m, 6 H); 1.55 to 1.69 (m, 2 H); 1.74 to 1.89 (m, 2 H); 1.93 to 2.04 (m, 1 H); 4.73 to 4.90 (m, 1 H); 7.01 (d, *J*=9.8 Hz, 1 H); 7.41 (dd, *J*=2.1 and 8.4 Hz, 1 H); 7.67 (d, *J*=8.6 Hz, 1 H); 8.05 (d, *J*=2.0 Hz, 1 H); 8.27 (d, *J*=9.8 Hz, 1 H); 12.67 (broad s, 1 H)
39	Retention time Tr (min) = 3,03; [M+H]+: m/z 568; [M-H]-: m/z 566	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.97 to 1.32 (m, 5 H); 1.47 to 1.68 (m, 5 H); 1.80 (m, 2 H); 2.25 to 2.37 (m, 6 H); 3.13 to 3.23 (m, 2 H); 3.37 to 3.49 (m, 1 H); 3.57 (m, 4 H); 6.71 to 6.82 (m, 1 H); 6.79 (d, *J*=10.0 Hz, 1 H); 7.25 (d, *J*=7.1 Hz, 1 H); 7.35 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.52 (d, *J*=8.6 Hz, 1 H); 7.91 (d, *J*=10.0 Hz, 1 H); 7.98 (d, *J*=2.0 Hz, 1 H); 10.80 (broad m, 1 H)
39b		^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.53 to 1.70 (m, 2 H); 2.28 to 2.37 (m, 6 H); 3.15 to 3.24 (m, 2 H); 3.52 to 3.63 (m, 4 H); 6.76 to 6.82 (m, 1 H); 7.48 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.58 (d, *J*=8.6 Hz, 1 H); 8.08 (d, *J*=2.0 Hz, 1 H); 10.86 (broad m, 1 H)
40	Retention time Tr (min) = 0.73; [M+H]+: m/z 569; [M-H]-: m/z 567	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.15 to 1.43 (m, 5 H); 1.45 to 1.53 (m, 1 H); 1.57 to 1.66 (m, 4 H); 1.78 to 1.86 (m, 2 H); 2.27 to 2.37 (m, 6 H); 3.19 (q, *J*=5.6 Hz, 2 H); 3.57 (t, *J*=4.8 Hz, 4 H); 4.66 to 4.75 (m, 1 H); 6.77 (broad s, 1 H); 7.02 (d, *J*=9.8 Hz, 1 H); 7.36 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.54 (d, *J*=8.3 Hz, 1 H); 8.00 (d, *J*=2.0 Hz, 1 H); 8.27 (d, *J*=9.8 Hz, 1 H); 10.81 (broad s, 1 H)
41	Retention time Tr (min) = 2.98; [M+H]+: m/z 527; [M-H]-: m/z 525	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.62 (m, 1 H); 1.76 (m, 1 H); 2.04 (m, 2 H); 2.30 (m, 2 H); 2.37 to 2.45 (m, 6 H); 3.23 to 3.28 (masked m, 2 H); 3.59 (t, *J*=4.6 Hz, 4 H); 4.92 (qd, *J*=7.1 and 7.3 Hz, 1 H); 6.77 (broad s, 1 H); 7.05 (d, *J*=9.8 Hz, 1 H); 7.42 (dd, *J*=2.1 and 8.4 Hz, 1 H); 7.57 (d, *J*=8.6 Hz, 1 H); 8.06 (d, *J*=2.2 Hz, 1 H); 8.28 (d, *J*=9.8 Hz, 1 H); 10.89 (broad s, 1 H)
42	Retention time Tr (min) = 0.75; [M+H]+: m/z 623; [M-H]-: m/z 621	^{1}H NMR Spectrum (400MHz, δ in ppm, DMSO-d_6):1.22 (m, 2 H); 1.33 (m, 2 H); 1.75 (d, *J*=13.2 Hz, 2 H); 1.94 (d, *J*=11.5 Hz, 2 H); 2.19 to 2.35 (m, 1 H); 2.36 to 2.45 (m, 6 H); 3.23 to 3.28 (masked m, 2 H); 3.59 (t, *J*=4.8 Hz, 4 H); 4.65 (m, 1 H); 6.76 (broad s, 1 H); 7.03 (d, *J*=9.8 Hz, 1 H);

		7.32 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.52 (d, *J*=8.6 Hz, 1 H); 7.96 (d, *J*=2.0 Hz, 1 H); 8.30 (d, *J*=9.8 Hz, 1 H); 10.87 (broad s, 1 H)
42b		^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.32 to 1.66 (m, 4 H); 1.99 (m, 2 H); 2.30 (m, 2 H); 2.37 to 2.45 (m, 1 H); 4.91 to 5.04 (m, 1 H); 7.09 (d, *J*=9.8 Hz, 1 H); 8.28 (d, *J*=9.8 Hz, 1 H)
43	Retention time Tr (min) = 4.56; [M+H]+: m/z 481; [M-H]-: m/z 479	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.20 (m, 2 H); 0.49 (m, 2 H); 1.06 (m, 1 H); 1.14 to 1.40 (m, 5 H); 1.42 to 1.65 (m, 3 H); 1.72 to 1.84 (m, 2 H); 2.37 (d, *J*=7.1 Hz, 2 H); 4.60 to 4.73 (m, 1 H); 7.02 (d, *J*=9.8 Hz, 1 H); 7.41 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.66 (d, *J*=8.6 Hz, 1 H); 8.06 (d, *J*=2.0 Hz, 1 H); 8.28 (d, *J*=9.8 Hz, 1 H); 12.30 (broad s, 1 H)
43b		^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): -0.03 to 0.03 (m, 2 H); 0.27 to 0.32 (m, 2 H); 0.81 to 0.93 (m, 1 H); 2.20 (d, *J*=7.1 Hz, 2 H); 7.48 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.63 (dd, *J*=0.5 and 8.6 Hz, 1 H); 8.18 (dd, *J*=0.5 and 2.0 Hz, 1 H); 12.24 (broad m, 1 H)
44	Retention time Tr (min) = 0.97; [M+H]+: m/z 439; [M-H]-: m/z 437	^{1}H NMR Spectrum (400MHz, δ in ppm, DMSO-d_6): 0.92 to 0.98 (m, 4 H); 1.60 (m, 1 H); 1.75 (m, 1 H); 2.01 (m, 3 H); 2.27 (m, 2 H); 4.90 (quin, *J*=7.3 Hz, 1 H); 7.06 (d, *J*=9.8 Hz, 1 H); 7.47 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.69 (d, *J*=8.6 Hz, 1 H); 8.11 (d, *J*=2.0 Hz, 1 H); 8.29 (d, *J*=9.8 Hz, 1 H); 12.67 (broad s, 1 H)
45	Retention time Tr (min) = 0.50; [M+H]+: m/z 612; [M-H]-: m/z 610	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6) Mixture of isomers 70% Trans 30% Cis: 1.12 to 1.65 (m, 4 H); 1.67 to 1.85 (m, 5H); 1.87 to 1.97 (m, 2 H); 2.35 to 2.45 (m, 6 H); 3.26 (masked m, 2 H); 3.51 to 3.68 (m, 5 H); 4.66 (m, 0.7 H); 4.98 (m, 0.3 H); 6.77 (broad s, 1 H); 6.98 to 7.06 (m, 1 H); 7.39 (m, 1 H); 7.56 (m, 1 H); 7.66 (d, *J*=8.6 Hz, 0.7 H); 7.74 (d, *J*=8.1 Hz, 0.3 H); 7.95 (d, *J*=2.0 Hz, 0.7 H); 8.03 (d, *J*=2.0 Hz, 0.3 H); 8.28 (d, *J*=9.5 Hz, 1 H); 10.88 (broad s, 1 H)
45b		^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6) mixture of isomers 70% trans (diaxial) and 30% cis (CHN ax – CHO eq) with: 1.29 to 2.23 (m, 8 H); 1.78 (s, 0.9 H); 1.80 (s, 2.1 H); 3.50 to 3.72 (m, 1 H); 4.94 (tt, *J*=4.2 and 10.3 Hz, 0.7 H); 5.14 (m, 0.3 H); 7.03 to 7.13 (m, 1 H); 7.79 to 7.90 (m, 1 H); 8.21 to 8.30 (m, 1 H)

46	Retention time Tr (min) = 1.05; [M+H]+: m/z 535; [M-H]-: m/z 533	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.90 to 0.98 (m, 4 H); 1.14 (m, 2 H); 1.31 (m, 2 H); 1.69 (d, *J*=12.2 Hz, 2 H); 1.87 (d, *J*=10.5 Hz, 2 H); 1.98 (m, 1 H); 2.24 (m, 1 H); 4.51 (m, 1 H); 7.03 (d, *J*=9.8 Hz, 1 H); 7.35 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.64 (d, *J*=8.6 Hz, 1 H); 8.02 (d, *J*=2.0 Hz, 1 H); 8.31 (d, *J*=9.8 Hz, 1 H); 12.66 (broad s, 1 H)
46b	Retention time Tr (min) = 3.86; [M+H]+: m/z 467; [M-H]-: m/z 465	
47	Retention time Tr (min) = 0.51; [M+H]+: m/z 571; [M-H]-: m/z 569	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.24 (m, 2 H); 1.36 (m, 2 H); 1.75 (m, 2 H); 1.91 (m, 2 H); 2.35 to 2.45 (m, 6 H); 3.23 to 3.29 (masked m, 2 H); 3.47 (m, 1 H); 3.59 (t, *J*=4.6 Hz, 4 H); 4.57 (d, *J*=4.2 Hz, 1 H); 4.72 (m, 1 H); 6.79 (broad s, 1 H); 7.01 (d, *J*=9.8 Hz, 1 H); 7.40 (dd, *J*=2.1 and 8.4 Hz, 1 H); 7.56 (d, *J*=8.6 Hz, 1 H); 7.96 (d, *J*=2.0 Hz, 1 H); 8.27 (d, *J*=9.8 Hz, 1 H); 10.87 (broad s, 1 H)
47b		^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.29 to 1.43 (m, 2 H); 1.49 to 1.63 (m, 2 H); 1.82 to 1.92 (m, 2 H); 2.09 to 2.22 (m, 2 H); 3.58 (m, 1 H); 4.59 (d, *J*=3.9 Hz, 1 H); 4.98 (m, 1 H); 7.07 (d, *J*=10.0 Hz, 1 H); 8.26 (d, *J*=10.0 Hz, 1 H)
48	Retention time Tr (min) = 3.65; [M+H]+: m/z 397; [M-H]-: m/z 395	^{1}H NMR Spectrum (400MHz, δ in ppm, DMSO-d_6): 0.38 (q, *J*=4.2 Hz, 1 H); 0.49 (m, 1 H); 1.32 (m, 2 H); 1.86 (m, 2 H); 2.20 (m, 2 H); 5.25 (t, *J*=6.7 Hz, 1 H); 6.96 (d, *J*=9.8 Hz, 1 H); 7.28 (d, *J*=8.3 Hz, 1 H); 7.33 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.62 (s, 2 H); 7.90 (d, *J*=2.0 Hz, 1 H); 8.22 (d, *J*=9.8 Hz, 1 H)
48b		^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.44 (q, *J*=4.2 Hz, 1 H); 0.53 (m, 1 H); 1.33 to 1.44 (m, 2 H); 1.99 (d, *J*=14.9 Hz, 2 H); 2.23 to 2.37 (m, 2 H); 5.44 (t, *J*=6.7 Hz, 1 H); 7.03 (d, *J*=9.8 Hz, 1 H); 8.24 (d, *J*=9.8 Hz, 1 H)
49	Retention time Tr (min) = 0,68; [M+H]+: m/z 370; [M-H]-: m/z 368	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.66 to 1.78 (m, 2 H); 1.80 to 1.96 (m, 2 H); 2.16 to 2.31 (m, 2 H); 3.95 to 4.18 (m, 1 H); 6.76 (d, *J*=9.8 Hz, 1 H); 7.31 (d, *J*=8.6 Hz, 1 H); 7.37 (dd, *J*=1.8 and 8.6 Hz, 1 H); 7.72 (broad d, *J*=7.0 Hz, 1 H); 7.87 to 7.95 (m, 2 H); 8.04 (broad m, 2 H)

49b	Retention time Tr (min) = 0,70; [M+H]+: m/z 224; [M-H]-: m/z 222	
50	Retention time Tr (min) = 1.08; [M+H]+: m/z 479; [M-H]-: m/z 477	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.35 (q, *J*=3.9 Hz, 1 H); 0.47 (m, 1 H); 1.27 (m, 2 H); 1.72 to 2.03 (m, *J*=14.9 Hz, 4 H); 2.07 to 2.33 (m, 6 H); 3.35 to 3.47 (masked m, 1 H); 5.21 (t, *J*=6.8 Hz, 1 H); 6.98 (d, *J*=9.8 Hz, 1 H); 7.45 (dd, *J*=2.1 and 8.4 Hz, 1 H); 7.67 (d, *J*=8.3 Hz, 1 H); 8.16 (d, *J*=2.0 Hz, 1 H); 8.25 (d, *J*=9.8 Hz, 1 H); 12.25 (broad s, 1 H)
51	Retention time Tr (min) = 0.76; [M+H]+: m/z 417; [M-H]-: m/z 415	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.29 (d, *J*=8.6 Hz, 3 H); 1.43 to 1.76 (m, 3 H); 1.90 to 2.18 (m, 2 H); 4.50 to 4.88 (m, 2 H); 7.07 (d, *J*=9.8 Hz, 1 H); 7.27 (d, *J*=8.6 Hz, 1 H); 7.31 (dd, *J*=1.7 and 8.3 Hz, 1 H); 7.61 (s, 2 H); 7.83 (d, *J*=2.0 Hz, 1 H); 8.29 (d, *J*=10.0 Hz, 1 H)
51b		^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.32 to 1.53 (m, 3 H); 1.56 to 1.79 (m, 3 H); 2.12 (m, 1 H); 2.30 (m, 1 H); 4.61 to 4.87 (m, 1 H); 5.01 to 5.17 (m, 1 H); 7.14 (d, *J*=9.8 Hz, 1 H); 8.30 (d, *J*=9.8 Hz, 1 H)
52	Retention time Tr (min) = 0.97; [M+H]+: m/z 485; [M-H]-: m/z 483	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.95 (m, 4 H); 1.07 to 1.33 (m, 3 H); 1.43 (m, 2 H); 1.62 (m, *J*=15.7 Hz, 1 H); 1.85 (m, 1 H); 1.93 to 2.12 (m, 2 H); 4.46 to 4.78 (m, 2 H); 7.08 (d, *J*=9.8 Hz, 1 H); 7.44 (dd, *J*=2.0 and 8.3 Hz, 1 H); 7.68 (d, *J*=8.3 Hz, 1 H); 8.08 (d, *J*=2.0 Hz, 1 H); 8.32 (d, *J*=9.8 Hz, 1 H); 12.67 (broad s, 1 H)
53	Retention time Tr (min) = 0,89; [M+H]+: m/z 438; [M-H]-: m/z 436	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.90 to 0.99 (m, 4 H); 1.61 to 1.73 (m, 2 H); 1.77 to 1.90 (m, 2 H); 1.94 to 2.04 (m, 1 H); 2.12 to 2.24 (m, 2 H); 3.95 to 4.07 (m, 1 H); 6.75 (d, *J*=9.8 Hz, 1 H); 7.45 (dd, *J*=1.8 and 8.4 Hz, 1 H); 7.63 to 7.72 (m, 2 H); 7.93 (d, *J*=9.8 Hz, 1 H); 8.12 (d, *J*=1.8 Hz, 1 H); 12.66 (broad m, 1 H)
54	Retention time Tr (min) = 1.03; [M+H]+: m/z 465; [M-H]-: m/z 463	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.34 (q, *J*=4.3 Hz, 1 H); 0.47 (m, 1 H); 0.95 (m, 4 H); 1.27 (m, 2 H); 1.72 to 1.84 (m, 2 H); 1.98 (m, 1 H); 2.12 (m, 2 H); 5.20 (t, *J*=6.7 Hz, 1 H); 6.98 (d, *J*=9.8 Hz, 1 H); 7.45 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.68 (d, *J*=8.6 Hz, 1 H); 8.13 (d, *J*=2.0 Hz, 1 H); 8.24 (d, *J*=9.8 Hz, 1 H); 12.66 (broad s, 1 H)
55	Retention time	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.99 (t,

	Tr (min) = 0,71; [M+H]+: m/z 530; [M+2H]2+: m/z 265,5 (base peak) [M-H]-: m/z 528	*J*=7.2 Hz, 6 H); 1.04 to 1.33 (m, 3 H); 1.34 to 1.50 (m, 2 H); 1.56 to 1.70 (m, 1 H); 1.85 (d, *J*=6.1 Hz, 1 H); 1.95 to 2.10 (m, 1 H); 2.62 (q, *J*=7.1 Hz, 4 H); 3.40 (s, 2 H); 4.42 to 4.76 (m, 2 H); 7.08 (d, *J*=9.8 Hz, 1 H); 7.43 (dd, *J*=1.8 and 8.4 Hz, 1 H); 7.67 (d, *J*=8.4 Hz, 1 H); 8.10 (d, *J*=1.8 Hz, 1 H); 8.32 (d, *J*=9.8 Hz, 1 H); 10.73 to 12.94 (very broad m, 1 H)
56	Retention time Tr (min) = 0,70; [M+H]+: m/z 571; [M+2H]2+: m/z 286 (base peak) [M-H]-: m/z 569	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.98 (t, *J*=7.1 Hz, 3 H); 1.08 to 1.33 (m, 3 H); 1.35 to 1.50 (m, 2 H); 1.63 (m, 1 H); 1.84 (m, 1 H); 2.04 (m, 1 H); 2.20 to 2.58 (partially masked m, 10 H); 3.20 to 3.40 (partially masked m, 2 H); 4.45 to 4.76 (m, 2 H); 7.08 (d, *J*=9.8 Hz, 1 H); 7.44 (dd, *J*=1.7 and 8.8 Hz, 1 H); 7.68 (d, *J*=8.8 Hz, 1 H); 8.10 (d, *J*=1.7 Hz, 1 H); 8.32 (d, *J*=9.8 Hz, 1 H); 12.09 (broad m, 1 H)
57	Retention time Tr (min) = 0,71; [M+H]+: m/z 544; [M+2H]2+: m/z 272,5 (base peak) [M-H]-: m/z 542	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.10 to 1.32 (m, 3 H); 1.34 to 1.51 (m, 2 H); 1.58 to 1.68 (m, 1 H); 1.81 to 1.92 (m, 1 H); 1.96 to 2.11 (m, 1 H); 2.45 to 2.55 (partially masked m, 4 H); 3.34 (s, 2 H); 3.56 to 3.66 (m, 4 H); 4.48 to 4.78 (m, 2 H); 7.08 (d, *J*=9.8 Hz, 1 H); 7.44 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.68 (d, *J*=8.6 Hz, 1 H); 8.10 (d, *J*=2.0 Hz, 1 H); 8.32 (d, *J*=9.8 Hz, 1 H); 12.15 (broad m, 1 H)
58	Retention time Tr (min) = 0,71; [M+H]+: m/z 498; [M+2H]2+: m/z 249,5 (base peak) [M-H]-: m/z 496	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.61 (m, 1 H); 1.74 (m, 1 H); 1.95 to 2.09 (m, 2 H); 2.20 to 2.31 (m, 2 H); 2.53 (m, 4 H); 3.33 (s, 2 H); 3.60 (m, 4 H); 4.90 (m, 1 H); 7.06 (d, *J*=9.8 Hz, 1 H); 7.47 (dd, *J*=2.0 and 8.8 Hz, 1 H); 7.70 (d, *J*=8.8 Hz, 1 H); 8.13 (d, *J*=2.0 Hz, 1 H); 8.30 (d, *J*=9.8 Hz, 1 H); 12.14 (broad m, 1 H)
59	Retention time Tr (min) = 0,72; [M+H]+: m/z 583; [M+2H]2+: m/z 292 (base peak) [M-H]-: m/z 581	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.26 (m, 2 H); 0.39 (m, 2 H); 1.02 to 1.33 (m, 3 H); 1.35 to 1.50 (m, 2 H); 1.61 (d, *J*=3.2 Hz, 2 H); 1.79 to 1.92 (m, 1 H); 2.04 (m, 1 H); 2.45 to 2.59 (partially masked m, 8 H); 3.37 to 3.41 (m, 2 H); 4.46 to 4.75 (m, 2 H); 7.08 (d, *J*=9.8 Hz, 1 H); 7.44 (broad d, *J*=8.7 Hz, 1 H); 7.68 (d, *J*=8.7 Hz, 1 H); 8.10 (broad s, 1 H); 8.32 (d, *J*=9.8 Hz, 1 H); 12.12 (broad m, 1 H)
59b	Retention time Tr (min) = 0,10; [M+H]+: m/z 185;	
60	Retention time Tr (min) = 0,71;	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.20 to 0.30 (m, 2 H); 0.36 to 0.45 (m, 2 H); 1.54 to 1.66 (m, 2 H);

	[M+H]+: m/z 537; [M+2H]2+: m/z 269 (base peak) [M-H]-: m/z 535	1.69 to 1.81 (m, 1 H); 1.96 to 2.09 (m, 2 H); 2.22 to 2.31 (m, 2 H); 2.42 to 2.60 (partially masked m, 8 H); 3.18 to 3.46 (partially masked m, 2 H); 4.90 (m, 1 H); 7.06 (d,*J*=9.8 Hz, 1 H); 7.47 (dd, *J*=1.9 and 8.6 Hz, 1 H); 7.70 (d, *J*=8.6 Hz, 1 H); 8.13 (d, *J*=1.9 Hz, 1 H); 8.29 (d, *J*=9.8 Hz, 1 H); 11.23 to 13.22 (very broad m, 1 H)
61	Retention time Tr (min) = 0,86; [M+H]+: m/z 546; [M-H]-: m/z 544	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.60 (m, 1 H); 1.75 (m, 1 H); 1.96 to 2.10 (m, 2 H); 2.23 to 2.34 (m, 2 H); 3.03 to 3.19 (m, 8 H); 3.58 (s, 2 H); 4.91 (m, 1 H); 7.06 (d, *J*=9.8 Hz, 1 H); 7.48 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.71 (d, *J*=8.6 Hz, 1 H); 8.14 (d, *J*=2.0 Hz, 1 H); 8.30 (d, *J*=9.8 Hz, 1 H); 12.23 (broad m, 1 H)
62	Retention time Tr (min) = 3,10; [M+H]+: m/z 512; [M-H]-: m/z 510	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.54 to 1.66 (m, 1 H); 1.68 to 1.78 (m, 1 H); 1.82 (quin, *J*=5.9 Hz, 2 H); 1.95 to 2.10 (m, 2 H); 2.22 to 2.32 (m, 2 H); 2.75 to 2.85 (m, 4 H); 3.53 (s, 2 H); 3.60 to 3.65 (m, 2 H); 3.69 (t, *J*=5.9 Hz, 2 H); 4.90 (m, 1 H); 7.06 (d, *J*=9.8 Hz, 1 H); 7.47 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.70 (d, *J*=8.6 Hz, 1 H); 8.13 (d, *J*=2.0 Hz, 1 H); 8.30 (d, *J*=9.8 Hz, 1 H); 12.12 (broad m, 1 H)
62b	Retention time Tr (min) = 0,13; [M+H]+: m/z 160; [M-H]-: m/z 158	
63	Retention time Tr (min) = 0,91; [M+H]+: m/z 457; [M-H]-: m/z 455	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.61 (m, 1 H); 1.74 (m, 1 H); 1.92 to 2.09 (m, 2 H); 2.22 to 2.32 (m, 2 H); 2.73 (t, *J*=6.1 Hz, 2 H); 3.23 (s, 3 H); 3.65 (t, *J*=6.1 Hz, 2 H); 4.90 (m, 1 H); 7.06 (d, *J*=10.0 Hz, 1 H); 7.47 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.69 (d, *J*=8.6 Hz, 1 H); 8.12 (d, *J*=2.0 Hz, 1 H); 8.29 (d, *J*=10.0 Hz, 1 H); 12.41 (broad m, 1 H)
64	Retention time Tr (min) = 1,04; [M+H]+: m/z 532; [M-H]-: m/z 530	^{1}H NMR Spectrum (400 MHz, δ in ppm, DMSO-d_6): 1.51 to 1.80 (m, 4 H); 1.82 to 1.94 (m, 2 H); 1.96 to 2.10 (m, 2 H); 2.22 to 2.31 (m, 2 H); 2.62 (m, 2 H); 2.90 (t, *J*=11.7 Hz, 2 H); 3.50 (s, 2 H); 4.90 (m, 1 H); 7.06 (d, *J*=9.8 Hz, 1 H); 7.48 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.71 (d, *J*=8.6 Hz, 1 H); 8.14 (d, *J*=2.0 Hz, 1 H); 8.30 (d, *J*=9.8 Hz, 1 H); 12.19 (broad m, 1 H)

64b	Retention time Tr (min) = 0,13; [M+H]+: m/z 180; [M-H]-: m/z 178	

Example 65:

Rac-1-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea, 15/85 mixture of the cis and trans isomers (major)

a) 1-{6-[(6-{[3-Methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea may be prepared in a manner similar to that described for Example **2a**, but with 0.240 g of a 1/1 mixture of racemic cis- and trans-3-chloro-6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazine, dissolved in 12 cm³ of ethanol, followed by addition, at a temperature in the region of 20°C, of 0.457 g of 1-[2-(morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea (**2b**), 0.416 g of DL- dithiothreitol, and a solution of 0.061 g of potassium dihydrogen phosphate in 0.600 cm³ of distilled water. After stirring at reflux for 8 hours, the reaction medium is concentrated to dryness under reduced pressure (2.7 kPa). The residue is taken up in 40 cm³ of dichloromethane and the mixture obtained is washed successively with twice 30 cm³ of distilled water and 15 cm³ of saturated sodium chloride solution, and is then dried over anhydrous magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) to give 0.370 g of an orange-coloured foam. This orange foam is purified by flash chromatography on silica [eluent: dichloromethane/methanol/acetonitrile (90/5/5 by volume + 0.1 % $^{v}/_{v}$ of 20% aqueous ammonia solution)]. After concentrating the fractions under reduced pressure, 0.121 g of a 15/85 mixture of racemic cis- and trans-1-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea is obtained in the form of a white solid melting at 197.6°C, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz, δ in ppm, DMSO-d_6) mixture of isomers 85% H1-ax 15% H1-eq with 0.71 (d, *J*=6.3 Hz, 0.45 H); 0.81 (d, *J*=6.6 Hz, 2.55 H); 0.72 to 1.80 (m, 7 H); 1.85 to 1.94 (m, 2 H); 2.36 to 2.44 (m, 6 H); 3.26 (partially masked m, 2 H); 3.59 (m, 4H); 4.64 (m, 0.85 H); 5.07 (m, 0.15 H); 6.78 (broad t, *J*=6.1 Hz, 1 H); 7.01 (d, *J*=10.0 Hz, 0.85 H); 7.03 (d, *J*=10.0 Hz, 0.15 H); 7.34 (dd, *J*=2.0 and 8.6 Hz, 0.85 H); 7.37 (dd, *J*=2.0 and 8.6 Hz, 0.15 H); 7.54 (d, *J*=8.6 Hz, 1 H); 7.96 (d, *J*=2.0 Hz, 0.85 H); 8.03 (d, *J*=2.0 Hz, 0.15 H); 8.25 (d, *J*=10.0 Hz, 0.15 H); 8.27 (d, *J*=10.0 Hz, 0.85 H); 10.90 (broad m, 1 H).

MASS SPECTRUM ES+/-: [M+H]+: m/z 569; [M-H]-: m/z 567.

b) The 1/1 mixture of racemic cis- and trans-3-chloro-6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazine may be prepared in a manner similar to that described in Example **1c**, but starting with 0.628 g of a 1/1 mixture of racemic cis- and trans-3-methyl-cyclohexanol dissolved in 6 cm^3 of tetrahydrofuran under a stream of argon, to which is added, at a temperature in the region of 0°C, 0.220 g of sodium hydride at 60% in oil. The reaction medium is maintained at a temperature in the region of 0°C for 15 minutes, followed by addition of 0.650 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine. After stirring at a temperature in the region of 20°C for 24 hours, 10 cm^3 of saturated aqueous ammonium chloride solution and 20 cm^3 of ethyl acetate are added. After separating the two phases, the organic phase is washed successively with twice 10 cm^3 of distilled water and 15 cm^3 of saturated sodium chloride solution and is then dried over anhydrous magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) to give 0.950 g of a 1/1 mixture of racemic cis- and trans-3-chloro-6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazine in the form of a brown oil, the characteristics of which are as follows:

MASS SPECTRUM ES+: [M+H]+: m/z 267.

Example 66:

Rac-N-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide, 15/85 mixture of the cis and trans isomers (major)

a) The 15/85 mixture of the cis and trans isomers of racemic N-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide may be prepared in a manner similar to that described for Example **2a**, but starting with 0.500 g of N-(6-sulfanyl-1,3-benzothiazol-2-yl)cyclopropanecarboxamide, 0.616 g of DL-dithiothreitol, a solution of 0.090 g of potassium dihydrogen phosphate in 1 cm^3 of distilled water, 0.355 g of a 1/1 mixture of racemic cis- and trans-3-chloro-6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazine (**65b**) and 18 cm^3 of ethanol. After stirring at reflux for 8 hours, followed by work-up and purification by flash chromatography on silica [eluent: dichloromethane/methanol/acetonitrile (90/5/5 by volume)], 0.198 g of a 15/85 mixture of the cis and trans isomers of racemic N-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide is obtained in the form of a white solid melting at 216.5°C, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz, **δ** in ppm, DMSO-d_6) mixture of isomers 85% H1-ax - 15% H1-eq with 0.70 (d, *J*=6.4 Hz, 0.45 H); 0.78 (d, *J*=6.4 Hz, 2.55 H); 0.72 to 1.78 (m, 11 H); 1.85 (m, 2 H); 1.97 (m, 1 H); 4.62 (m, 0.85 H); 5.03 (m, 0.15 H); 7.01 (d, *J*=9.8 Hz, 0.85 H); 7.03 (d, *J*=9.8 Hz, 0.15 H); 7.39 (dd, *J*=2.0 and 8.6 Hz, 0.85 H); 7.41 (dd, *J*=2.0 and 8.6 Hz, 0.15 H); 7.66 (d, *J*=8.6 Hz, 1 H); 8.02 (d, *J*=2.0 Hz, 0.85 H); 8.09 (d, *J*=2.0 Hz, 0.15 H); 8.26 (d, *J*=9.8 Hz, 0.15 H); 8.28 (d, *J*=9.8 Hz, 0.85 H); 12.67 (broad m, 1 H).

MASS SPECTRUM ES+/-: [M+H]+: m/z 481; [M-H]-: m/z 479.

b) N-(6-Sulfanyl-1,3-benzothiazol-2-yl)cyclopropanecarboxamide may be prepared in a manner similar to that described in Example **2b**, but starting with 14.0 g of 2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl thiocyanate, 22.44 g of DL-dithiothreitol, a solution of 0.235 g of potassium

dihydrogen phosphate in 60 cm³ of distilled water and 450 cm³ of ethanol. After stirring at reflux for 5 hours, the reaction medium is poured into 700 cm³ of ice-water under a stream of argon. The yellow solid formed is filtered off on VF3, washed with twice 70 cm³ of ice-water and then oven-dried under reduced pressure (2.7 kPa) at 40°C for 24 hours, to give 12.74 g of N-(6-sulfanyl-1,3-benzothiazol-2-yl)cyclopropanecarboxamide in the form of a yellow solid, the characteristics of which are as follows:

MASS SPECTRUM ES+/-: [M+H]+: m/z 251; [M-H]-: m/z 249.

c) 2-[(Cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl thiocyanate may be prepared in a manner similar to that described in Example **1a**, but starting with 15.0 g of 2-amino-1,3-benzothiazol-6-yl thiocyanate, 7.88 cm³ of cyclopropanecarboxylic acid chloride and 150 cm³ of pyridine. After stirring for 5 hours at a temperature in the region of 20°C, the reaction medium is poured into 500 cm³ of ice-water. The solid formed is filtered off on a VF3 filter and then washed with 5 times 70 cm³ of ice-water, followed by oven-drying under reduced pressure (2.7 kPa) at 40°C for 10 hours, to give 19 g of 2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl thiocyanate in the form of a pink solid, the characteristics of which are as follows:

MASS SPECTRUM ES+/-: [M+H]+: m/z 276; [M-H]-: m/z 274.

Example 67:

1-[6-({6-[(4-methylcyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}-sulfanyl)-1,3-benzothiazol-2-yl]-3-[2-(morpholin-4-yl)ethyl]urea, 15/85 mixture of the cis and trans isomers (major)

a) The 15/85 mixture of cis- and trans-1-[6-({6-[(4-methylcyclohexyl)oxy]-[1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]-3-[2-(morpholin-4-yl)ethyl]urea may be prepared in a manner similar to that described for Example **2a**, but starting with 0.876 g of 1-[2-(morpholin-4-yl)-ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea (**2b**), 0.798 g of DL-dithiothreitol, a solution of 0.117 g of potassium dihydrogen phosphate in 1.15 cm³ of distilled water, 0.460 g of a 1/1 mixture of cis- and trans-3-chloro-6-(4-

methylcyclohexyloxy)-1,2,4-triazolo[4,3-b]pyridazine and 23 cm³ of ethanol. After stirring at reflux for 16 hours, followed by work-up and purification by flash chromatography on silica [eluent: dichloromethane/methanol/acetonitrile (90/5/5 by volume + 0.1 % $^{v}/_{v}$ of 20% aqueous ammonia solution)], 0.261g of a 15/85 mixture of racemic cis- and trans-1-[6-({6-[(4-methylcyclohexyl)oxy]-[1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]-3-[2-(morpholin-4-yl)ethyl]urea is obtained in the form of a white solid melting at 155.9°C, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz, **δ** in ppm, DMSO-d_6) mixture of isomers 85% H1-ax - 15% H1-eq with: 0.86 (d, *J*=6.4 Hz, 3 H); 0.88 to 0.93 (m, 2 H); 1.17 to 1.63 (m, 5 H); 1.76 to 1.93 (m, 2 H); 2.35 to 2.45 (m, 6 H); 3.26 (partially masked m, 2 H); 3.59 (m, 4 H); 4.40 to 4.57 (m, 1 H); 6.78 (broad m, 1 H); 7.00 (d, *J*=9.8 Hz, 0.85 H); 7.04 (d, *J*=9.8 Hz, 0.15 H); 7.31 (dd, *J*=2.0 and 8.6 Hz, 0.85 H); 7.40 (dd, *J*=2.0 and 8.6 Hz, 0.15 H); 7.53 (d, *J*=8.6 Hz, 0.85 H); 7.55 (d, *J*=8.6 Hz, 0.15 H); 8.00 (d, *J*=2.0 Hz, 0.85 H); 8.04 (d, *J*=2.0 Hz, 0.15 H); 8.25 (d, *J*=9.8 Hz, 0.15 H); 8.27 (d, *J*=9.8 Hz, 0.85 H); 10.91 (broad m, 1 H).

MASS SPECTRUM ES+/-: [M+H]+: m/z 569; [M-H]-: m/z 567.

b) The 1/1 mixture of cis- and trans-3-chloro-6-(4-methylcyclohexyloxy)-1,2,4-triazolo[4,3-b]pyridazine may be prepared in a manner similar to that described in Example **1c**, but starting with 0.628 g of a 1/1 mixture of racemic cis- and trans-4-methyl cyclohexanol, 6 cm³ of tetrahydrofuran, 0.220 g of sodium hydride at 60% in oil and 0.650 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]-pyridazine. After stirring at a temperature in the region of 20°C for 24 hours, followed by work-up, 0.880 g of a 1/1 mixture of cis- and trans-3-chloro-6-(4-methyl-cyclohexyloxy)-1,2,4-triazolo[4,3-b]pyridazine is obtained in the form of a brown oil that solidifies, the characteristics of which are as follows:

MASS SPECTRUM ES+: [M+H]+: m/z 267.

Example 68:

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(piperidin-1-yl)azetidine-1-carboxamide

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(piperidin-1-yl)azetidine-1-carboxamide may be prepared in a manner similar to that of Example **5**, but starting with 185 mg of phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate **(4)** in 10 cm^3 of THF and 10 cm^3 of DMF with 75 mg of 1-(azetidin-3-yl)piperidine dihydrochloride and 0.160 cm^3 of triethylamine after reaction for 66 hours at 20°C. 155 mg of N-(6-{[6-(cyclohexyloxy)[1,2,4]-triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(piperidin-1-yl)azetidine-1-carboxamide are thus obtained in the form of a pale yellow solid, the characteristics of which are as follows:

^{1}H NMR SPECTRUM (400 MHz, DMSO-d_6, δppm): 1.13 to 1.67 (m, 14 H); 1.81 (m, 2 H); 2.24 (broad m, 4 H); 2.99 to 3.20 (broad m, 1 H); 3.70 to 4.15 (broad m, 4 H); 4.64 to 4.74 (m, 1 H); 7.01 (d, *J*=9.8 Hz, 1 H); 7.37 (dd, *J*=2.0 and 8.3 Hz, 1 H); 7.55 (d, *J*=8.3 Hz, 1 H); 8.00 (broad s, 1 H); 8.27 (d, *J*=9.8 Hz, 1 H); 11.32 (broad m, 1 H).

MASS SPECTRUM (Electrospray on WATERS UPLC – SQD):

[M+H]+: m/z 565; [M-H]-: m/z 563.

Example 69:

N-[6-({6-[(4-methylcyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}-sulfanyl)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide, 15/85 mixture of the cis and trans isomers (major)

The 85/15 mixture of cis- and trans-N-[6-({6-[(4-methylcyclohexyl)oxy][1,2,4]-triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]cyclopropane-carboxamide may be prepared in a manner similar to that described for Example **2a**, but starting with 0.592 g of N-(6-sulfanyl-1,3-benzothiazol-2-yl)-cyclopropanecarboxamide (**66b**), 0.729 g of DL-dithiothreitol, a solution of 0.107 g of potassium dihydrogen phosphate in 1.05 cm^3 of distilled water,

0.420 g of a 1/1 mixture of 3-chloro-6-(4-methyl-cyclohexyloxy)-1,2,4-triazolo-[4,3-b]pyridazine (**67b**) and 20 cm³ of ethanol. After stirring at reflux for 16 hours, followed by work-up and purification by flash chromatography on silica [eluent: dichloromethane/methanol/acetonitrile (90/5/5 by volume)], 0.336 g of a 15/85 mixture of the cis and trans isomers of N-[6-({6-[(4-methylcyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzo-thiazol-2-yl]cyclopropanecarboxamide is obtained in the form of a white solid melting at 230°C, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz, **δ** in ppm, DMSO-d_6) mixture of isomers 85% H1-ax - 15% H1-eq with: 0.72 to 0.99 (m, 6 H); 0.82 (d, *J*=6.6 Hz, 2.55 H); 0.88 (d, *J*=6.6 Hz, 0.45 H); 1.06 to 1.59 (m, 5 H); 1.82 (d, *J*=9.0 Hz, 2 H); 1.94 to 2.04 (m, 1 H); 4.35 to 4.51 (m, 1 H); 7.00 (d, *J*=9.8 Hz, 0.85 H); 7.04 (d, *J*=9.8 Hz, 0.15 H); 7.35 (dd, *J*=2.0 and 8.6 Hz, 0.85 H); 7.45 (dd, *J*=2.0 and 8.6 Hz, 0.15 H); 7.66 (d, *J*=8.6 Hz, 0.85 H); 7.68 (d, *J*=8.6 Hz, 0.15 H); 8.06 (d, *J*=2.0 Hz, 0.85 H); 8.11 (d, *J*=2.0 Hz, 0.15 H); 8.26 (d, *J*=9.8 Hz, 0.15 H); 8.28 (d, *J*=9.8 Hz, 0.85 H); 12.68 (broad m, 1 H).

MASS SPECTRUM ES+/-: [M+H]+: m/z 481; [M-H]-: m/z 479.

Example 70:

N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide may be prepared in a manner similar to that described in Example **5**, but starting with 150 mg of phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)carbamate **(4)**, 65 mg of 2-oxa-6-aza-spiro[3.3]heptane monooxalate, 0.144 cm³ of triethylamine and 10 cm³ of tetrahydrofuran. After stirring for 15 hours at a temperature in the region of 20°C, followed by work-up, 0.056 g of N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo-[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-oxa-6-azaspiro[3.3]-

heptane-6-carboxamide are obtained in the form of a white solid, the characteristics of which are as follows:

MASS SPECTRUM ES+/-: [M+H]+: m/z 524; [M-H]-: m/z 522.

^{1}H NMR spectrum (400 MHz, **δ** in ppm, DMSO-d_6): 1.15 to 1.42 (m, 5 H); 1.49 (m, 1 H); 1.61 (m, 2 H); 1.81 (m, 2 H); 4.20 (broad s, 4 H); 4.66 (s, 4 H); 4.68 to 4.74 (m, 1 H); 7.01 (d, J=9.8 Hz, 1 H); 7.37 (dd, J=2.0 and 8.6 Hz, 1 H); 7.55 (broad d, J=8.6 Hz, 1 H); 8.00 (d, J=2.0 Hz, 1 H); 8.27 (d, J=9.8 Hz, 1 H); 11.36 (broad m, 1 H).

2-Oxa-6-azaspiro[3.3]heptane monooxalate may be prepared as described by Georg Wuitschik, Mark Rogers-Evans, Andreas Buckl, Maurizio Bernasconi, Moritz Märki, Thierry Godel, Holger Fischer, Björn Wagner, Isabelle Parrilla, Franz Schuler, Josef Schneider, André Alker, W. Bernd Schweizer, Klaus Müller, and Erick M. Carreira, Angew. Chem. Int. Ed. 2008, 47, 4512 –4515.

Example 71:

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(morpholin-4-yl)azetidine-1-carboxamide

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(morpholin-4-yl)azetidine-1-carboxamide may be prepared in a manner similar to that of Example **5**, but starting with 182 mg of phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate (**4**) in 10 cm^3 of THF, 106 mg of 4-(azetidin-3-yl)morpholine dihydrochloride and 0.167 cm^3 of triethylamine, after reaction for 22 hours at 20°C. 60 mg of N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]-pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(morpholin-4-yl)azetidine-1-carboxamide are thus obtained in the form of a white solid, the characteristics of which are as follows:

^{1}H NMR SPECTRUM (400 MHz, DMSO-d_6, δppm): 1.11 to 1.42 (m, 5 H); 1.50 (m, 1 H); 1.62 (m, 2 H);1.82 (m, 2 H); 2.31 (m, 4 H); 3.09 to 3.19 (m, 1 H); 3.59 (m, 4 H); 3.85 (m, 2 H); 4.04 (m, 2 H); 4.63 to4.78 (m, 1 H); 7.01 (d,

J=9.8 Hz, 1 H); 7.36 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.52 (broad d, *J*=8.6 Hz, 1 H);7.98 (d, *J*=2.0 Hz, 1 H); 8.26 (d, *J*=9.8 Hz, 1 H); 11.38 (broad m, 1 H).

MASS SPECTRUM (Electrospray WATERS ZQ):

[M+H]+: m/z 567; [M-H]-: m/z 565.

Example 72:

Rac-N-{6-[(6-{[trans-2-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide

a) rac-N-{6-[(6-{[trans-2-Methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide may be prepared in a manner similar to that described for Example **2a**, but starting with 0.636 g of N-(6-sulfanyl-1,3-benzothiazol-2-yl)cyclopropanecarboxamide (**66b**), 0.784 g of DL-dithiothreitol, a solution of 0.115 g of potassium dihydrogen phosphate in 1.27 cm³ of distilled water, 0.428 g of a 1/1 mixture of racemic cis- and trans-3-chloro-6-(2-methyl-cyclopentyloxy)-1,2,4-triazolo-[4,3-b]pyridazine and 23 cm³ of ethanol. After stirring at reflux for 16 hours, followed by work-up and purification by flash chromatography on silica [eluent: dichloromethane/methanol/acetonitrile (90/5/5 by volume)], 0.260 g of rac-N-{6-[(6-{[trans-2-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide is obtained in the form of a white solid melting at 197.7°C, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.89 (d, *J*=7.1 Hz, 3 H); 0.92 to 1.00 (m, 4 H); 1.06 to 1.21 (m, 1 H); 1.46 to 1.69 (m, 3 H); 1.78 to 2.12 (m, 4 H); 4.45 to 4.56 (m, 1 H); 7.03 (d, *J*=9.8 Hz, 1 H); 7.43 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.68 (d, *J*=8.6 Hz, 1 H); 8.09 (d, *J*=2.0 Hz, 1 H); 8.27 (d, *J*=9.8 Hz, 1 H); 12.67 (broad m, 1 H).

MASS SPECTRUM ES+/-: [M+H]+: m/z 467; [M-H]-: m/z 465.

b) The 1/1 mixture of racemic cis- and trans-3-chloro-6-(2-methylcyclopentyloxy)-1,2,4-triazolo[4,3-b]pyridazine may be prepared in a manner similar to that described in Example **1c**, but starting with 0.678 g of a

1/1 mixture of cis- and trans- 2-methylcyclopentanol, 10 cm³ de tetrahydrofuran, 0.271 g of sodium hydride at 60% in oil, and 0.800 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine. After stirring at a temperature in the region of 20°C for 24 hours, followed by work-up, 1.033 g of a 1/1 mixture of racemic cis- and trans-de 3-chloro-6-(2-methyl-cyclopentyloxy)-1,2,4-triazolo-[4,3-b]pyridazine are obtained in the form of a brown oil, the characteristics of which are as follows:

MASS SPECTRUM ES+: [M+H]+: m/z 253.

Example 73:

Rac-1-{6-[(6-{[trans-2-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea

rac-1-{6-[(6-{[trans-2-Methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea may be prepared in a manner similar to that described for Example **2a**, but starting with 0.609 g of 1-[2-(morpholin-4-yl)ethyl]-3-(6-sulfanyl-1,3-benzothiazol-2-yl)urea (**2b**), 0.555 g of DL-dithiothreitol, a solution of 0.081 g of potassium dihydrogen phosphate in 0.85 cm³ of distilled water, 0.303 g of a 1/1 mixture of racemic cis- and trans-3-chloro-6-(2-methyl-cyclopentyloxy)-1,2,4-triazolo-[4,3-b]pyridazine (**72b**) and 17 cm³ of ethanol. After stirring at reflux for 16 hours, followed by work-up and purification by flash chromatography on silica [eluent: dichloromethane/ methanol/acetonitrile (90/5/5 by volume + 0.1 % $^{v}/_{v}$ of 20% aqueous ammonia solution)], 0.223 g of rac-1-{6-[(6-{[trans-2-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzo-thiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea is obtained in the form of a pale yellow solid melting at 203.3°C, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz, δ in ppm, DMSO-d_6): 0.92 (d, *J*=7.1 Hz, 3 H); 1.16 (m, 1 H); 1.50 to 1.69 (m, 3 H); 1.79 to 2.12 (m, 3 H); 2.37 to 2.44 (m, 6 H); 3.26 (partially masked m, 2 H); 3.59 (m, 4 H); 4.52 to 4.60 (m, 1 H); 6.79 (broad m, 1 H); 7.03 (d, *J*=9.8 Hz, 1 H); 7.37 (dd, *J*=2.0 and 8.5 Hz, 1 H); 7.55

(d, *J*=8.5 Hz, 1 H); 8.03 (d, *J*=2.0 Hz, 1 H); 8.26 (d, *J*=9.8 Hz, 1 H); 10.90 (broad m, 1 H).

MASS SPECTRUM ES+/-: [M+H]+: m/z 555; [M-H]-: m/z 553.

Example 74:

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxyazetidine-1-carboxamide

N-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxyazetidine-1-carboxamide may be prepared in a manner similar to that of Example **5**, but starting with 192 mg of phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate (**4**) in 5 cm^3 of dimethylformamide, 69 mg of 3-methoxyazetidine hydrochloride and 0.078 cm^3 of triethylamine, after reaction for 20 hours at 20°C. 120 mg of N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxyazetidine-1-carboxamide are thus obtained in the form of an off-white solid, the characteristics of which are as follows:

^{1}H NMR SPECTRUM (400 MHz, DMSO-d_6, δ ppm): 1.14 to 1.42 (m, 5 H); 1.44 to 1.53 (m, 1 H); 1.61 (m, 2 H); 1.81 (m, 2 H); 3.21 (s, 3 H); 3.83 (m, 2 H); 4.13 to 4.30 (m, 3 H); 4.64 to 4.74 (m, 1 H); 7.02 (d, *J*=9.8 Hz, 1 H); 7.37 (dd, *J*=2.0 and 8.6 Hz, 1 H); 7.54 (broad d, *J*=8.6 Hz, 1 H); 8.00 (d, *J*=2.0 Hz, 1 H); 8.27 (d, *J*=9.8 Hz, 1 H); 11.36 (broad m, 1 H).

MASS SPECTRUM (Electrospray WATERS ZQ):

[M+H]+: m/z 512; [M-H]-: m/z 510.

Example 75:

1-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-oxetan-3-ylurea

1-(6-{[6-(Cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-oxetan-3-ylurea may be prepared in a manner similar to that of Example **5**, but starting with 191 mg of phenyl (6-{[6-(cyclo-

hexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-carbamate (**4**) in 3 cm^3 of dimethylformamide, 40 mg of oxetan-3-amine, after reaction for 20 hours at 20°C. 95 mg of 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo-[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-oxetan-3-ylurea are thus obtained in the form of a white solid, the characteristics of which are as follows:

^{1}H NMR SPECTRUM (400 MHz, DMSO-d_6, δppm): 1.12 to 1.43 (m, 5 H); 1.47 to 1.54 (m, 1 H); 1.62 (m, 2 H); 1.83 (m, 2 H); 4.47 (t, *J*=6.4 Hz, 2 H); 4.67 to 4.76 (m, 3 H); 4.77 to 4.86 (m, 1 H); 7.01 (d, *J*=9.8Hz, 1 H); 7.35 (dd, *J*=1.8 and 8.4 Hz, 1 H); 7.52 (broad m, 2 H); 7.97 (broad s, 1 H); 8.26 (d, *J*=9.8 Hz, 1 H); 10.99 (broad m, 1 H).

MASS SPECTRUM (Electrospray on WATERS UPLC – SQD):

[M+H]+: m/z 498; [M-H]-: m/z 496.

Example 76:

Rac-1-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea, 2/3 mixture of the racemic cis and trans isomers (major)

a) The 2/3 mixture of the racemic cis and trans isomers of 1-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea may be prepared in a manner similar to that described for Example **2a**, but starting with 0.643 g of 1-(6-mercapto-benzothiazol-2-yl)-3-(2-morpholin-4-yl-ethyl)-urea (2b), 0.586 g of DL-dithiothreitol, a solution of 0.086 g of potassium dihydrogen phosphate in 0.95 cm^3 of distilled water, 0.320 g of a 1/1 mixture of the racemic cis and trans isomers of 3-chloro-6-(3-methyl-cyclopentyloxy)-1,2,4-triazolo[4,3-b]-pyridazine and 19 cm^3 of ethanol. After stirring at reflux for 16 hours, followed by work-up and purification by flash chromatography on silica [eluent: dichloromethane/methanol/acetonitrile (90/5/5 by volume with 0.1% $^v/_v$ of 20% aqueous ammonia solution)], 0.065 g of a 2/3 mixture of the racemic cis and trans isomers of 1-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyrid-

azin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea is obtained in the form of a white solid melting at 174.7°C, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz, **δ** in ppm, DMSO-d_6) 2/3 - 1/3 mixture of isomers, with: 0.90 (d, *J*=6.8 Hz, 1 H); 0.94 (d, *J*=6.6 Hz, 2 H); 1.00 to 1.35 (m, 2 H); 1.57 to 2.16 (m, 5 H); 2.36 to 2.44 (m, 6 H); 3.26 (partially masked m, 2 H); 3.59 (m, 4 H); 5.05 (m, 0.66 H); 5.11 (m, 0.34 H); 6.79 (broad m, 1 H); 7.00 (d, *J*=9.8 Hz, 0.34 H); 7.02 (d, *J*=9.8 Hz, 0.66 H); 7.38 (split dd, *J*=2.0 and 8.6 Hz, 1 H); 7.54 (d, *J*=8.6 Hz, 1 H); 8.04 (d, *J*=2.0 Hz, 1 H); 8.25 (split d, *J*=9.8 Hz, 1 H); 10.92 (broad m, 1 H).

MASS SPECTRUM ES+/-: [M+H]+: m/z 555; [M-H]-: m/z 553.

b) The 1/1 mixture of the racemic cis and trans isomers of 3-chloro-6-(3-methyl-cyclopentyloxy)-1,2,4-triazolo[4,3-b]pyridazine may be prepared in a manner similar to that described in Example **1c**, but starting with 0.678 g of a 1/1 mixture of racemic cis and trans-3-methylcyclopentanol isomers, 10 cm^3 of tetrahydrofuran, 0.271 g of sodium hydride at 60% in oil and 0.800 g of 3,6-dichloro[1,2,4]triazolo[4,3-b]pyridazine. After stirring at a temperature in the region of 20°C for 24 hours followed by work-up, 0.860g of a 1/1 mixture of the racemic cis and trans isomers of 3-chloro-6-(3-methyl-cyclopentyloxy)-1,2,4-triazolo[4,3-b]pyridazine is obtained in the form of a brown oil, the characteristics of which are as follows:

MASS SPECTRUM ES+/-: [M+H]+: m/z 253.

Example 77:

Rac-N-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide, 2/3 mixture of the racemic cis and trans isomers (major)

The 2/3 mixture of the racemic cis and trans isomers of N-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide may be prepared in a manner similar to that described for Example **2a**, but starting with 0.505 g of N-(6-

sulfanyl-1,3-benzothiazol-2-yl)cyclopropanecarboxamide (**66b**), 0.622 g of DL-dithiothreitol, a solution of 0.091 g of potassium dihydrogen phosphate in 1.01 cm³ of distilled water, 0.340 g of a 1/1 mixture of the racemic cis and trans isomers of 3-chloro-6-(3-methyl-cyclopentyloxy)-1,2,4-triazolo[4,3-b]-pyridazine (**76b**) and 23 cm³ of ethanol. After stirring at reflux for 16 hours, followed by work-up and purification by flash chromatography on silica [eluent: dichloromethane/methanol/acetonitrile (90/5/5 by volume)], 0.172 g of a 2/3 mixture of the racemic cis and trans isomers of N-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide is obtained in the form of a white solid melting at 98°C, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz, **δ** in ppm, DMSO-d_6) 2/3 - 1/3 mixture of isomers, with: 0.84 to 0.97 (m, 7 H); 0.99 to 1.30 (m, 2 H); 1.54 to 2.14 (m, 6 H); 5.03 (m, 0.66 H); 5.10 (m, 0.34 H); 7.00 (d, *J*=9.8 Hz, 0.34 H); 7.02 (d, *J*=9.8 Hz, 0.66 H); 7.41 (split dd, *J*=2.0 and 8.6 Hz, 1 H); 7.65 (broad d, *J*=8.6 Hz, 1 H); 8.08 (broad s, 1 H); 8.26 (split d, *J*=9.8 Hz, 1 H); 12.64 (broad m, 1 H).

MASS SPECTRUM ES+/-: [M+H]+: m/z 467; [M-H]-: m/z 465.

Example 78: Pharmaceutical composition

Tablets corresponding to the following formula were prepared:
Product of Example 1..... 0.2 g
Excipient for a finished tablet weighing ..... 1 g
(details of the excipient: lactose, talc, starch, magnesium stearate).

Example 79: Pharmaceutical composition

Tablets corresponding to the following formula were prepared:
Product of Example 4 ..... 0.2 g
Excipient for a finished tablet weighing ..... 1 g
(details of the excipient: lactose, talc, starch, magnesium stearate).

Examples 1 and 4 are taken as examples of pharmaceutical preparation, this preparation possibly being performed, if desired, with other products illustrated in the present patent application.

Pharmacological section:

Experimental protocols

I) Expression and Purification of MET, cytoplasmic domain

Expression as Baculovirus:

The recombinant DNA His-Tev-MET (956-1390) in pFastBac (Invitrogen) is transfected into insect cells and, after several viral amplification steps, the final baculovirus stock is tested for expression of the protein of interest.

After infection for 72 hours at 27°C with the recombinant virus, the SF21 cell cultures are harvested by centrifugation and the cell pellets are stored at -80°C.

Purification:

The cell pellets are resuspended in lysis buffer (buffer A [50 mM HEPES, pH 7.5, 250 mM NaCl, Glycerol 10%, TECP 1 mM]; + Roche Diagnostics EDTA-free protease inhibitor cocktail, ref. 1873580), stirred at 4°C until homogeneous, and then mechanically lysed using a "Dounce" machine.

After centrifugation, the lysis supernatant is incubated for 2 hours at 4°C with nickel chelate resin (His-Trap 6 Fast Flow ™, GE HealthCare). After washing with 20 volumes of buffer A, the suspension is packed into a column, and the proteins are eluted with a gradient of buffer B (buffer A + 290 mM imidazole).

The fractions containing the protein of interest in the light of the electrophoretic analysis (SDS PAGE) are pooled, concentrated by ultrafiltration (10 kDa cut-off) and injected onto an exclusion chromatography column (Superdex ™ 200, GE HealthCare) equilibrated with buffer A.

After enzymatic cleavage of the Histidine tag, the protein is reinjected onto a new IMAC Nickel Chelate chromatography column (His-Trap 6 Fast Flow ™, GE HealthCare) equilibrated with buffer A. The fractions eluted with a gradient of buffer B and containing the protein of interest after electrophoresis (SDS PAGE) are finally pooled and stored at -80°C.

For the production of autophosphorylated protein, the preceding fractions are incubated for 1 hour at room temperature after addition of ATP 2 mM, $MgCl_2$ 2 mM, and Na_3VO_4 4 mM. After stopping the reaction with 5 mM of EDTA, the reaction mixture is injected onto a HiPrep desalting column (GE HealthCare) pre-equilibrated with buffer A + Na_3VO_4 4 mM, and the fractions containing the protein of interest (SDS PAGE analysis) are pooled and stored at -80°C. The degree of phosphorylation is checked by mass spectrometry (LC-MS) and by peptide mapping.

II) Tests A and B

A) **Test A:** HTRF MET test in 96-well format

In a final volume of 50 µl of enzymatic reaction, MET 5 nM final is incubated in the presence of the test molecule (for a final concentration range of 0.17 nM to 10 µM, DMSO 3% final) in MOPS 10 mM pH 7.4, DTT 1 mM, 0.01% Tween 20 buffer. The reaction is initiated with the substrate solution to obtain final concentrations of poly-(GAT) 1 µg/ml, ATP 10 µM and $MgCl_2$ 5 mM. After incubation for 10 minutes at room temperature, the reaction is stopped with a mix of 30 µl to obtain a final solution of Hepes 50 mM pH 7.5, potassium fluoride 500 mM, 0.1% BSA and EDTA 133 mM in the presence of 80 ng of streptavidin 61SAXLB Cis-Bio Int. and 18 ng of anti-phosphotyrosine Mab PT66-Europium Cryptate per well. After incubation for 2 hours at room temperature, the reading is taken at two wavelengths, 620 nm and 665 nm, on a reader for the TRACE / HTRF technique and the percentage of inhibition is calculated from the 665/620 ratios.

The results obtained via this test A for the products of formula (I) illustrated in the experimental section are such that the IC50 is less than 500 nM and especially less than 100 nM.

B) **Test B:** Inhibition of autophosphorylation of MET; ELISA technique (pppY1230,1234,1235)

a) Cell lysates: Inoculated MKN45 cells in 96-well plates (Cell coat BD polylysine) to a rate of 20 000 cells/well in 200 µl in RPMI medium + 10% FCS + 1% L-glutamine. Leave to adhere for 24 hours in an incubator.

The cells are treated the day after inoculation with the products at six concentrations in duplicate for 1 hour. At least three control wells are treated with the same amount of final DMSO.

Product dilution: Stock at 10 mM in pure DMSO - range from 10 mM to 30 µM with an increment of 3 in pure DMSO - Intermediate 50-fold dilutions in the culture medium, followed by removal of 10 µl added directly to the cells (200 µl): final range from 10 000 to 30 nM.

At the end of incubation, delicately remove the supernatant and rinse with 200 µl of PBS. Next, place 100 µl of lysis buffer directly in the wells on ice and incubate at 4°C for 30 minutes. Lysis buffer: 10 mM Tris-HCl pH 7.4, 100 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1% Triton X-100, 10% glycerol, 0.1% SDS, 0.5% deoxycholate, 20 mM NaF, 2 mM Na_3VO_4, 1 mM PMSF and anti-protease cocktail.

The 100 µl of lysates are transferred into a V-bottomed polypropylene plate and ELISA is performed directly or the plate is frozen at –80°C.

b) ELISA PhosphoMET BioSource Kit KHO0281

Add 70 µl of kit dilution buffer + 30 µL of cell lysates or 30 µl of lysis buffer for the blanks to each well of the kit plate. Incubate for 2 hours with gentle rocking at room temperature.

Rinse the wells four times with 400 µl of kit washing buffer. Incubate with 100 µl of anti-phospho MET antibody for 1 hour at room temperature.

Rinse the wells four times with 400 µL of kit washing buffer. Incubate with 100 µl of anti-rabbit HRP antibody for 30 minutes at room temperature (except for the wells with chromogen alone).

Rinse the wells four times with 400 µl of kit washing buffer. Introduce 100 µl of chromogen and incubate for 30 minutes in the dark at room temperature.

Stop the reaction with 100 µl of stop solution. Take the reading without delay, at 450 nM 0.1 second on a Wallac Victor plate reader.

C) **Test C:** Measurement of the cell proliferation via a 14C-thymidine pulse

The cells are inoculated in Cytostar 96-well plates in 180 µl for 4 hours at 37°C and 5% CO_2: HCT116 cells at a rate of 2500 cells per well in DMEM medium + 10% foetal calf serum + 1% L-Glutamine and MKN45 cells at a rate of 7500 cells per well in RPMI medium + 10% foetal calf serum + 1% L-Glutamine. After these 4 hours of incubation, the products are added in 10 µl as a 20-fold concentrated solution according to the dilution method cited for ELISA. The products are tested at 10 concentrations in duplicate from 10 000 nM to 0.3 nM with an increment of 3.

After 72 hours of treatment, add 10 µl of 14C-thymidine at 10 µCi/ml to obtain 0.1 µCi per well. The incorporation of 14C-thymidine is measured on a Micro-Beta machine (Perkin-Elmer) after 24 hours of pulse and 96 hours of treatment.

All the test steps are automated on BIOMEK 2000 or TECAN stations.

The results obtained via this test B for the products of formula (I) illustrated in the experimental section are such that the IC50 is less than 10 µM and especially less than 1 µM.

The results obtained for the products illustrated in the experimental section are given in the table of pharmacological results hereinbelow, as follows:
for test A, the + sign corresponds to less than 500 nM and the ++ sign corresponds to less than 100 nM,
for test B, the + sign corresponds to less than 500 nM and the ++ sign corresponds to less than 100 nM,
for test C, the + sign corresponds to less than 10 µM and the ++ sign corresponds to less than 1 µM.

Table of pharmacological results:

Ex. number	test A	test B	test C
1	++	++	++
2	++	++	++
3	++	++	++
4	++	+	++
5	++	++	++
6	++		++
7	++	++	++
8	++		++

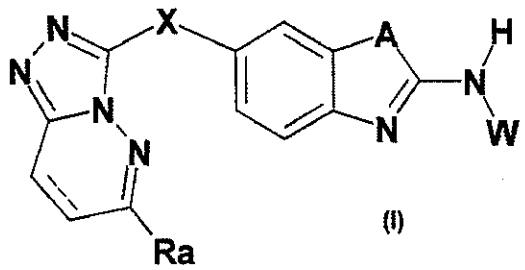
9	++	++	++
10	++	++	++
11	++	++	++
12	++	++	++
13	++	++	++
14	++	++	++
15	++	++	++
16	++	+	++
17	++	++	++
18	++	++	++
19	++	++	++
20	++	+	++
21	++	++	++
22	++		++
23	++	++	++
24	++	++	++
25	++	++	++
26	++	++	++
27	++	++	++
28	++	++	++
29	++	++	++
30	++	++	++
31	++		++
32	++	++	++
33	++	+	++
34	++	++	++
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	++	++	++

CLAIMS

1- Products of formula (I):



(I)

in which

---- represents a single or double bond;

Ra represents a radical -O-cycloalkyl, or a radical -NH- cycloalkyl, both optionally substituted;

X represents S, SO or SO2;

A represents NH or S;

W represents a hydrogen atom; an alkyl radical optionally substituted with alkoxy, heterocycloalkyl or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical, optionally substituted with a halogen atom or a radical cycloalkyl, NR3R4, alkoxy, hydroxyl, phenyl, heteroaryl or heterocycloalkyl, which are themselves optionally substituted;
- an alkoxy radical optionally substituted with NR3R4, alkoxy, hydroxyl or heterocycloalkyl; a radical O-phenyl or a radical O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 4;
- or the radical NR1R2 in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical, a heterocycloalkyl radical or an alkyl radical and the other from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical optionally substituted with one or more radicals, which may be identical or different, chosen from the following radicals: hydroxyl, alkoxy, heteroaryl, heterocycloalkyl, NR3R4, phenyl, optionally

substituted or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, with the optional S possibly being in the form SO or SO2; this radical, including the possible NH it contains, being optionally substituted;

with R3 and R4, which may be identical or different, representing a hydrogen atom, an alkyl radical, a cycloalkyl radical, a heterocycloalkyl radical, a heteroaryl radical or a phenyl radical, all optionally substituted with one or more radicals, which may be identical or different, chosen from the following radicals: optionally substituted hydroxyl, alkoxy, heteroaryl, heterocycloalkyl, NH2, NHAlk, N(Alk)2 or phenyl; or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, with the optional S possibly being in the form SO or SO2; this radical, including the possible NH it contains, being optionally substituted;

all the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl and phenyl radicals defined above, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, being optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkoxy, -O-CO-R5, -COOH, COOR5, -CONH2, CONHR5, NH2, NHR5, NR5R5', -NH-CO-R5 and alkyl, cycloalkyl, heterocycloalkyl, CH2-heterocycloalkyl, phenyl, CH2-phenyl, CO-phenyl, heteroaryl and S-heteroaryl radicals, such that in the latter radicals, the alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl radicals are themselves optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkyl and alkoxy containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2,

all the cycloalkyl, heterocycloalkyl, heteroaryl and phenyl radicals defined above being furthermore optionally substituted with a radical Si(alk)3;

it being possible for all the cycloalkyl and heterocycloalkyl radicals defined above to be optionally substituted on one of the carbons of the ring by a spirocycloalkyl or spiroheterocycloalkyl radical or optionally on two of the carbons of the ring by a fused cycloalkyl or heterocycloalkyl radical;

R5 and R5', which may be identical or different, represent an alkyl or cycloalkyl radical containing not more than 6 carbon atoms;

alk represents an alkyl radical containing not more than 4 carbon atoms;

it being understood that W does not represent H when A represents S, X represents S, Ra represents the unsubstituted O-cyclohexyl radical or the unsubstituted NH-cyclohexyl radical and ---- represents a double bond,

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

2- Products of formula (I) as defined in Claim 1, in which

---- represents a single or double bond;

Ra represents a radical -O-cycloalkyl or a radical -NH-cycloalkyl optionally substituted;

X represents S, SO or SO_2;

A represents NH or S;

W represents a hydrogen atom, an alkyl radical optionally substituted with alkoxy, heterocycloalkyl or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical, optionally substituted with a halogen atom or a radical cycloalkyl, NR3R4, alkoxy, hydroxyl, phenyl, heteroaryl or heterocycloalkyl, which are themselves optionally substituted;
- an alkoxy radical optionally substituted with NR3R4, alkoxy, hydroxyl or heterocycloalkyl; a radical O-phenyl or a radical O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 4;

- or the radical NR1R2 in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical and the other from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical, a heterocycloalkyl radical or an alkyl radical optionally substituted with one or more radicals, which may be identical or different, chosen from the following radicals: hydroxyl, alkoxy, heteroaryl, heterocycloalkyl, NR3R4, phenyl, optionally substituted or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, with the optional S possibly being in the form SO or SO2, this radical, including the possible NH it contains, being optionally substituted;

with R3 and R4, which may be identical or different, representing a hydrogen atom, an alkyl radical, a cycloalkyl radical, a heterocycloalkyl radical, a heteroaryl radical or a phenyl radical, all optionally substituted with one or more radicals, which may be identical or different, chosen from the following radicals: hydroxyl, alkoxy, heteroaryl, heterocycloalkyl, NH2, NHAlk, N(Alk)2 or phenyl, optionally substituted; or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, with the optional S possibly being in the form SO or SO2, this radical, including the possible NH it contains, being optionally substituted;

all the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl and phenyl radicals defined above, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, being optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkoxy, -O-CO-R5, NH2, NHalk, N(alk)2 and alkyl, cycloalkyl, heterocycloalkyl, CH2-heterocycloalkyl, phenyl, CH2-phenyl, CO-phenyl, heteroaryl and S-heteroaryl radicals, such that in the latter radicals, the alkyl,

cycloalkyl, heterocycloalkyl, phenyl and heteroaryl radicals are themselves optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, oxo, alkyl and alkoxy containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2;

R5 represents an alkyl or cycloalkyl radical containing not more than 6 carbon atoms;

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

3- Products of formula (I) as defined in any one of the claims, in which ----- , Ra and X have the values defined in any one of the other claims, and:

A represents NH or S;

W represents a hydrogen atom; an alkyl radical optionally substituted with alkoxy, heterocycloalkyl or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical optionally substituted with a halogen atom or a radical cycloalkyl, NR3R4, alkoxy, hydroxyl, phenyl or heterocycloalkyl, which are themselves optionally substituted;
- an alkoxy radical optionally substituted with NR3R4, alkoxy, hydroxyl or heterocycloalkyl; a radical O-phenyl or a radical O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 4;
- or the radical NR1R2, in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom or an alkyl radical and the other from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical, a heterocycloalkyl radical or an alkyl radical optionally substituted with an alkoxy or heterocycloalkyl radical, or NR3R4; or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

- with NR3R4 such that R3 and R4, which may be identical or different, represent a hydrogen atom or an alkyl radical or a heterocycloalkyl radical, all optionally substituted with one or more radicals, which may be identical or different, chosen from alkoxy or heterocycloalkyl radicals or NH2, NHAlk or N(Alk)2; or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a 3- to 10-membered cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

all the cycloalkyl, heterocycloalkyl and phenyl radicals, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, defined above, being optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, alkoxy, NH2, NHalk, N(alk)2 and alkyl, heterocycloalkyl, CH2-heterocycloalkyl, phenyl, CH2-phenyl and heteroaryl radicals, such that in the latter radicals, the alkyl, heterocycloalkyl, phenyl and heteroaryl radicals are themselves optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, alkyl and alkoxy radicals containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2;

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

4- Products of formula (I) as defined in any one of the other claims, in which ---- , Ra and X have the values defined in any one of the other claims, and:

A represents NH or S;

W represents a hydrogen atom; an alkyl radical optionally substituted with a heterocycloalkyl radical or NR3R4; or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical optionally substituted with a radical NR3R4, or alkoxy;

- a radical O-phenyl or O-(CH2)n-phenyl, with phenyl optionally substituted and n represents an integer from 1 to 2;

- or the radical NR1R2, in which R1 and R2 are such that one from among R1 and R2 represents a hydrogen atom, a cycloalkyl radical or an alkyl radical and the other from among R1 and R2 represents a hydrogen atom, an alkyl radical optionally substituted with a heterocyclic radical or NR3R4, or alternatively R1 and R2 form, with the nitrogen atom to which they are attached, a cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

with NR3R4 such that R3 and R4, which may be identical or different, represent a hydrogen atom or an alkyl radical or alternatively R3 and R4 form, with the nitrogen atom to which they are attached, a cyclic radical optionally containing one or more other heteroatoms chosen from O, S, N and NH, this radical, including the possible NH it contains, being optionally substituted;

all the cycloalkyl, heterocyclic and phenyl radicals, and also the cyclic radicals that may be formed by R1 and R2 or R3 and R4 with the nitrogen atom to which they are attached, defined above, being optionally substituted with one or more radicals chosen from halogen atoms and the following radicals: hydroxyl, alkoxy, NH2, NHalk, N(alk)2 and alkyl and phenyl radicals, the latter radicals themselves being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, alkyl and alkoxy radicals containing from 1 to 4 carbon atoms, NH2, NHalk and N(alk)2;

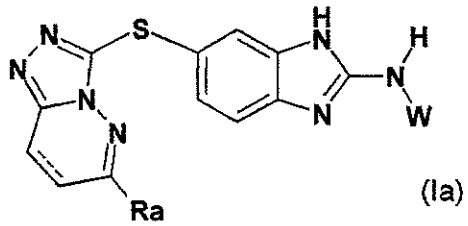
the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

5- Products of formula (I) as defined in any one of the other claims, in which A represents NH, the substituents ---- , Ra, X and W being chosen from all the values defined for these radicals in any one of the other claims, the said products of formula (I) being in any possible racemic, enantiomeric or

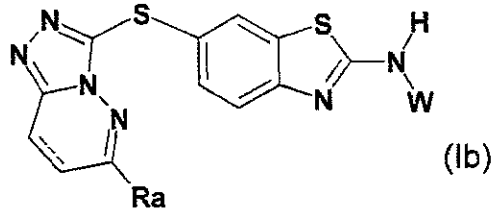
diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

6- Products of formula (I) as defined in any one of the other claims, in which A represents S, the substituents ---- , Ra, X and W being chosen from all the values defined for these radicals in any one of the other claims, the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

7- Products of formula (I) as defined in any one of the other claims, corresponding to formula (Ia) or (Ib):



(Ia)

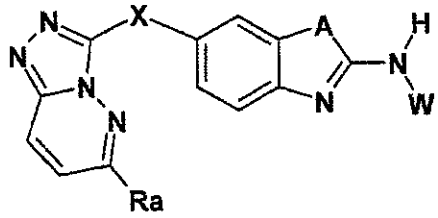


(Ib)

in which ---- , Ra and W are chosen from the meanings indicated in any one of the other claims,

the said products of formula (Ia) and (Ib) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (Ia) and (Ib).

8- Products of formula (I) as defined in any one of the other claims, in which ---- represents a double bond, corresponding to the products of formula (I''):

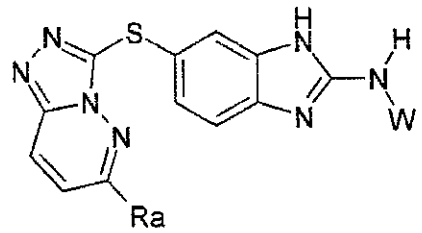


(I")

in which the substituents Ra, X, A and W have the meanings indicated in any one of the other claims,

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

9- Products of formula (Ia) as defined in any one of the other claims, in which ---- represents a double bond, corresponding to the products of formula (I"a):

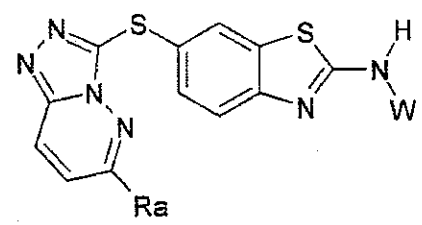


(I"a)

in which Ra and W are chosen from the meanings indicated in any one of the other claims,

the said products of formula (I"a) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I"a).

10- Products of formula (Ib) as defined in any one of the other claims, in which ---- represents a double bond, corresponding to the products of formula (I"b):



(I"b)

in which Ra and W are chosen from the meanings indicated in any one of the other claims,

the said products of formula (I''b) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I''b).

11- Products of formula (I) as defined in any one of the preceding claims, in which

---- represents a single or double bond

Ra represents a radical -O-cycloalkyl, or a radical -NH-cycloalkyl; optionally substituted with a hydroxyl, alkoxy or -O-CO-R5 radical;

X represents S;

A represents S;

W represents a hydrogen atom or an alkyl radical optionally substituted with heterocycloalkyl or the radical COR in which R represents:

- a cycloalkyl radical or an alkyl radical, optionally substituted with a radical NR3R4, or alkoxy;
- a radical O-phenyl;
- or the radical NR1R2 in which R1 and R2 are such that one represents a hydrogen atom and the other represents an alkyl radical optionally substituted with a heterocycloalkyl radical;

with NR3R4 such that R3 and R4, which may be identical or different, represent a hydrogen atom or an alkyl radical;

R5 represents an alkyl or cycloalkyl radical containing at most 6 carbon atoms;

the said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

12- Products of formula (I) as defined in any one of the other claims, corresponding to the following formulae:

- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- 1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea
- N-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- N-[6-({6-[(trans-4-hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- 1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- phenyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)carbamate
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(pyrrolidin-1-yl)ethyl]urea
- 6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-N-[2-(pyrrolidin-1-yl)ethyl]-1,3-benzothiazol-2-amine

- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-methoxyacetamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2,N^2-dimethylglycinamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methylbutanamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide
- 6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine
- N-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- N-(6-{[6-(cyclopentyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- 6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-amine
- N-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- trans-4-{[3-({2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}-sulfanyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]amino}cyclohexyl cyclopropanecarboxylate
- N-[6-({6-[(trans-4-hydroxycyclohexyl)amino][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]acetamide
- 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclopropyl[1,2,4]triazolo-[4,3-b]pyridazin-6-amine
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide
- N-(6-{[6-(cyclopropylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2,N^2-dimethylglycinamide

- 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclohexyl-7,8-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-6-amine
- ethyl (6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)carbamate
- 2-chloro-N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)acetamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2-cyclopropylglycinamide
- 6-[(6-{[4-(trifluoromethyl)cyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-amine
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-N^2,N^2-diethylglycinamide
- N-(6-{[6-(cycloheptyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- 1-(6-{[6-(cyclohexylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[3-(morpholin-4-yl)propyl]urea
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[3-(morpholin-4-yl)propyl]urea
- 1-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-[2-(morpholin-4-yl)ethyl]urea
- 1-[2-(morpholin-4-yl)ethyl]-3-{6-[(6-{[4-(trifluoromethyl)cyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-cyclopropylacetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- rac-cis/trans-N-{4-[(3-{[2-({[2-(morpholin-4-yl)ethyl]carbamoyl}amino)-1,3-benzothiazol-6-yl]sulfanyl}[1,2,4]triazolo[4,3-b]pyridazin-6-yl)oxy]cyclohexyl}acetamide

- N-{6-[(6-{[4-(trifluoromethyl)cyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- 1-[6-({6-[(trans-4-hydroxycyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]-3-[2-(morpholin-4-yl)ethyl]urea
- 6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-amine
- 3-[(2-amino-1,3-benzothiazol-6-yl)sulfanyl]-N-cyclobutyl[1,2,4]triazolo-[4,3-b]pyridazin-6-amine
- N-(6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)cyclobutanecarboxamide
- rac-6-({6-[(trans-2-fluorocyclohexyl)oxy][1,2,4]triazolo[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-amine
- rac-N-{6-[(6-{[(trans-2-fluorocyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- N-(6-{[6-(cyclobutylamino)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- N-(6-{[6-(bicyclo[3.1.0]hex-3-yloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-sulfanyl}-1,3-benzothiazol-2-yl)cyclopropanecarboxamide
- rac-N^2,N^2-diethyl-N-[6-({6-[(trans-2-fluorocyclohexyl)oxy][1,2,4]triazolo-[4,3-b]pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]glycinamide
- rac-2-(4-ethylpiperazin-1-yl)-N-{6-[(6-{[trans-2-fluorocyclohexyl]oxy}-[1,2,4] triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}acetamide
- rac-N-{6-[(6-{[trans-2-fluorocyclohexyl]oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-2-(morpholin-4-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(morpholin-4-yl)acetamide
- rac-2-(4-cyclopropylpiperazin-1-yl)-N-{6-[(6-{[trans-2-fluorocyclohexyl]-oxy}[1,2,4]triazolo[4,3-b]pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(4-cyclopropylpiperazin-1-yl)acetamide

- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(1,1-dioxidothiomorpholin-4-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(1,4-oxazepan-4-yl)acetamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxypropanamide
- N-(6-{[6-(cyclobutyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-(3,3-difluoropiperidin-1-yl)acetamide
- rac-cis/trans-1-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]-pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea
- rac-cis/trans-N-{6-[(6-{[3-methylcyclohexyl]oxy}[1,2,4]triazolo[4,3-b]-pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- rac-cis/trans-1-[6-({6-[(4-methylcyclohexyl)oxy][1,2,4]triazolo[4,3-b]-pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(piperidin-1-yl)azetidine-1-carboxamide
- rac-cis/trans-N-[6-({6-[(4-methylcyclohexyl)oxy][1,2,4]triazolo[4,3-b]-pyridazin-3-yl}sulfanyl)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-(morpholin-4-yl)azetidine-1-carboxamide
- rac-N-{6-[(6-{[trans-2-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyrid-azin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide
- rac-1-{6-[(6-{[trans-2-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]pyrid-azin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea
- N-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-methoxyazetidine-1-carboxamide
- 1-(6-{[6-(cyclohexyloxy)[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl}-1,3-benzothiazol-2-yl)-3-oxetan-3-ylurea

- rac-cis/trans-1-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]-pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}-3-[2-(morpholin-4-yl)ethyl]urea
- rac-cis/trans-N-{6-[(6-{[3-methylcyclopentyl]oxy}[1,2,4]triazolo[4,3-b]-pyridazin-3-yl)sulfanyl]-1,3-benzothiazol-2-yl}cyclopropanecarboxamide

and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

13- Process for preparing the products of formula (I) as defined in any one of the other claims.

14- Process for preparing the products of formula (I) as defined in any one of the other claims, in which A represents NH.

15- Process for preparing the products of formula (I) as defined in any one of the other claims, in which A represents S.

16- As medicaments, the products of formula (I) as defined in any one of Claims 1 to **12**, and also the addition salts with pharmaceutically acceptable mineral and organic acids or with pharmaceutically acceptable mineral and organic bases of the said products of formula (I).

17- As medicaments, the products of formula (I) as defined in Claim **12**, and also the addition salts with pharmaceutically acceptable mineral and organic acids or with pharmaceutically acceptable mineral and organic bases of the said products of formula (I).

18- Pharmaceutical compositions containing, as active principle, at least one of the products of formula (I) as defined in any one of Claims 1 to **12**, or a pharmaceutically acceptable salt of this product or a prodrug of this product and a pharmaceutically acceptable support.

19- Use of the products of formula (I) as defined in any one of Claims 1 to **12**, or of pharmaceutically acceptable salts of these products, for the preparation of a medicament for inhibiting the activity of the kinase protein MET and mutant forms thereof.

20- Use as defined in Claim **19**, in which the kinase protein is in a cell culture.

21- Use as defined in Claim **19** or **20**, in which the kinase protein is in a mammal.

22- Use of a product of formula (I) as defined in any one of Claims 1 to **12**, for the preparation of a medicament for treating or preventing a disease chosen from the following group: blood vessel proliferation disorders, fibrotic disorders, "mesangial" cell proliferation disorders, metabolic disorders, allergies, asthmas, thromboses, nervous system diseases, retinopathy, psoriasis, rheumatoid arthritis, diabetes, muscle degeneration and cancers.

23- Use of a product of formula (I) as defined in any one of Claims 1 to **12**, for the preparation of a medicament for treating cancers.

24- Use according to **23**, for treating solid or liquid tumours.

25- Use according to **23** or **24**, for treating cancers that are resistant to cytotoxic agents.

26- Use according to one or more of Claims **23** and **24**, for treating primary tumours and/or metastases, in particular in stomach, liver, kidney, ovarian, bowel or prostate cancer, lung cancer (NSCLC and SCLC), glioblastomas, thyroid, bladder or breast cancers, melanomas, lymphoid or myeloid haematopoietic tumours, sarcomas, brain cancers, cancer of the larynx, cancer of the lymphatic system, bone cancers and pancreatic cancers.

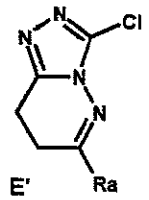
27- Use of the products of formula (I) as defined in Claims 1 to **12**, for the preparation of medicaments for cancer chemotherapy.

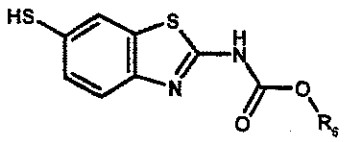
28- Use of the products of formula (I) as defined in Claims 1 to **12**, for the preparation of medicaments for cancer chemotherapy, alone or in combination.

29- Products of formula (I) as defined in any one of Claims 1 to **12**, as kinase inhibitors.

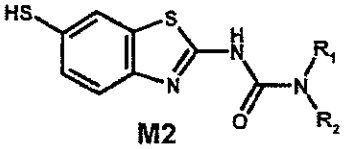
30- Products of formula (I) as defined in any one of Claims 1 to **12**, as MET inhibitors.

31- As novel industrial products, the synthetic intermediates of formulae E', M1, M2, M3 and N:

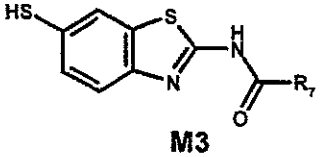




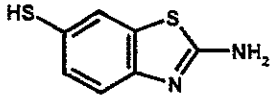
M1



M2



M3



N

in which R6 represents an alkyl radical optionally substituted with an NR3R4 (a -(CH2)n-NR3R4 radical), alkoxy, hydroxyl, heterocycloalkyl, phenyl or -(CH2)n-phenyl group, with phenyl being optionally substituted and n representing an integer from 1 to 4, such that OR6 represents the corresponding values of R as defined above; R7 represents a cycloalkyl or alkyl radical optionally substituted with an NR3R4, alkoxy or hydroxyl radical or a phenyl, heteroaryl or heterocycloalkyl radical, themselves optionally substituted as indicated in Claim 1; and Ra, R1, R2, R3 and R4 have the meanings indicated in Claim 1.