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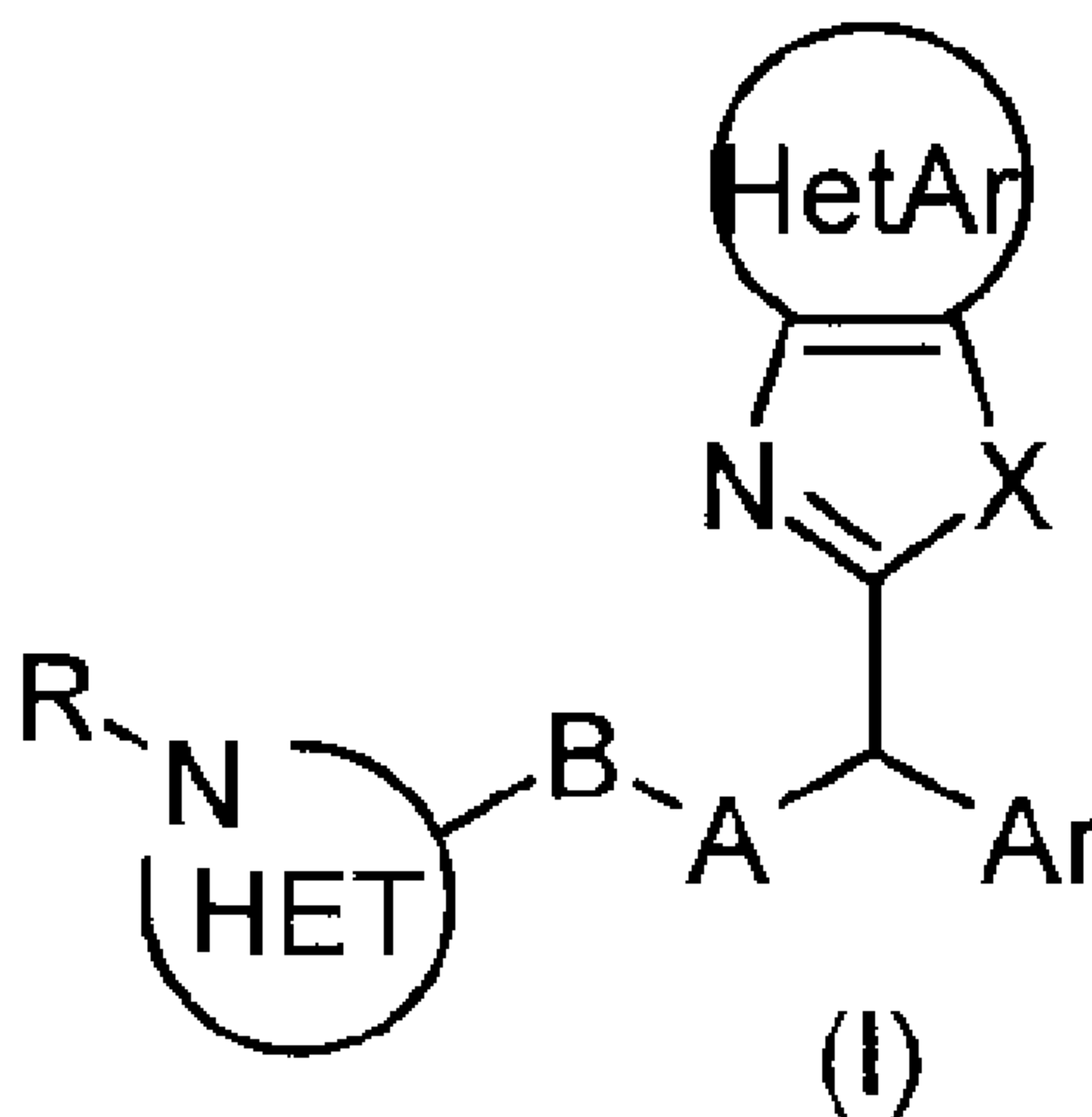
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(54) **Titre : UTILISATION DE DERIVES DE BENZAZOLE EN TANT QUE LIGANDS DES RECEPTEURS H4 DE L'HISTAMINE**
(54) **Title: BENZAZOLE DERIVATIVES AS HISTAMINE H4 RECEPTOR LIGANDS**



(57) **Abrégé/Abstract:**

The present patent application concerns new ligands of the H4-receptor of formula (I), their process of preparation and their therapeutic use.

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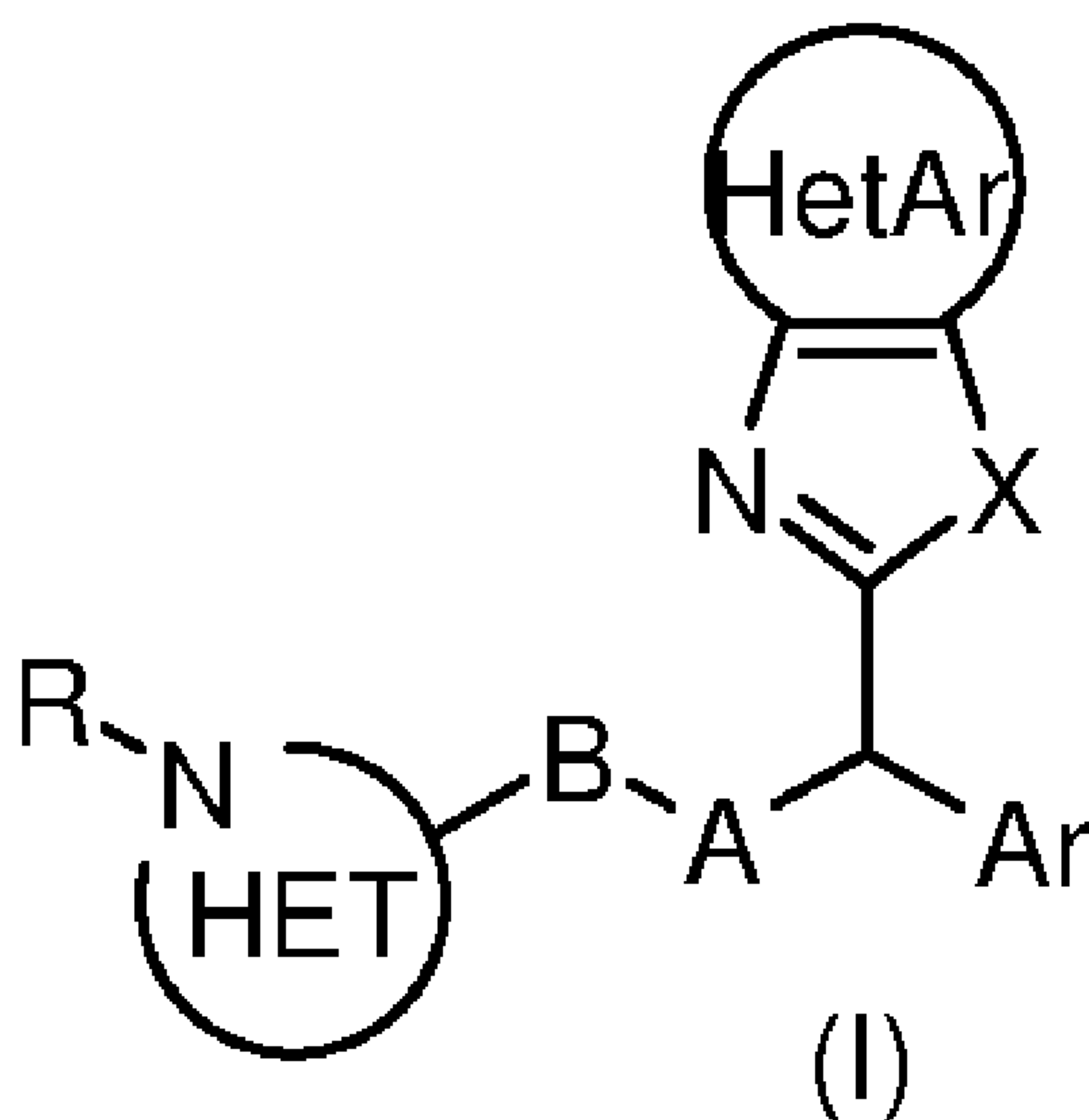
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(54) Title: BENZAZOLE DERIVATIVES AS HISTAMINE H4 RECEPTOR LIGANDS

(57) Abstract: The present patent application concerns new ligands of the H4-receptor of formula (I), their process of preparation and their therapeutic use.



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BENZAZOLE DERIVATIVES AS HISTAMINE H4 RECEPTOR LIGANDS

The present patent application concerns new ligands of the H4-receptor, their process of preparation and their therapeutic use.

5

Until recently, the pro-inflammatory actions of histamine were thought to be essentially mediated by the H1 receptor and H1 receptor antagonists have found large therapeutic applications in allergic manifestations like the anaphylactic shock, allergic rhinitis, dermatitis, pruritus, etc.

10

However these drugs essentially prevent the occurrence of major symptoms of these manifestations without modifying clearly the progressive development of the inflammatory process leading to chronic diseases like asthma in which, however, histamine release from mast-cells might represent an important trigger (reviewed in Galli et al, Nature, 2008, 454, 445).

15

The recent discovery of the histamine H4 receptor (H4R) has modified this landscape (reviewed in Thurmond et al, Nature Rev. Drug Disc., 2008, 7, 41). The H4R belongs to the superfamily of G-protein coupled heptahelical receptors and is expressed on the plasma membranes of a variety of immunocompetent/inflammatory cells, e.g. eosinophils, basophils, mast-cells or dendritic cells. The H4R has a chemotactic role, controlling the influx of e.g. mast-cells or eosinophils to inflammatory sites that is elicited by histamine release and, thereby plays a major role in the development of chronic inflammatory disorders. It also controls the activity of eosinophils and some classes of lymphocytes. Blockade of the H4R by antagonists or inverse agonists should therefore constitute a novel therapeutic approach in diseases like asthma, emphysema, allergic rhinitis, nasal congestion, bronchitis, chronic obstructive pulmonary disease, dermatitis, arthritis, psoriasis, colitis, etc. in which they could be used alone or in association with already used other classes of anti-inflammatory medications, namely H1R antagonists. In addition the utilisation of H4R antagonists/inverse agonists is also of potential interest in a variety of autoimmune diseases e.g. type I diabetes, Crohn's disease, multiple sclerosis, lupus, etc... The itch-preventing effect of some H4R antagonists in a rodent model (Bell et al, Br J Pharmacol, 2004, 142, 374) also suggests the use of these agents in pruritus, a manifestation only imperfectly controlled by available medications, namely H1R antagonists.

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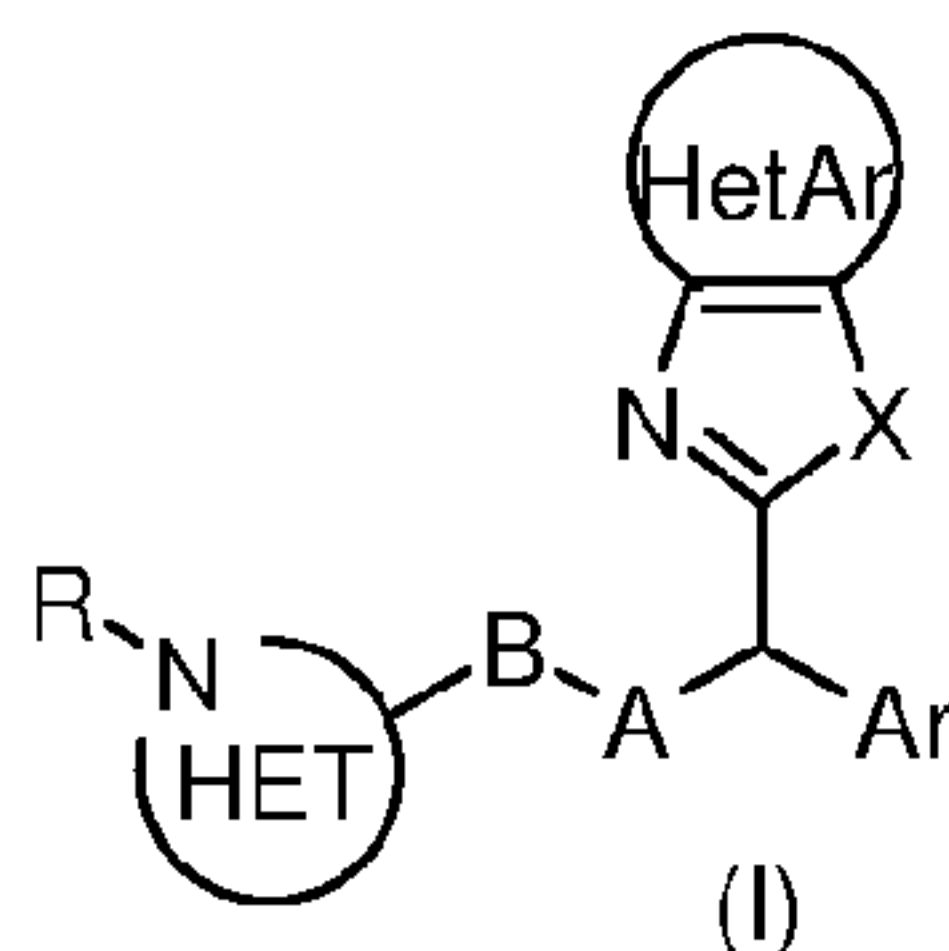
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H4R antagonists/inverse agonists have not yet reached clinical uses and there is therefore a need for compounds displaying high potency and safety. In the present application a novel chemical class of H4R ligands is disclosed.

The instant invention thus relates to novel benzazoles derivatives as H4 receptor ligands, to their preparation and to their application in therapeutics.

According to a first object, the present invention concerns new compounds of
5 formula (I):



wherein:

X represents NR', S or O;

HetAr represents a phenyl or heteroaryl, optionally substituted with one or more
10 substituents chosen from halogen, OR'', alkyl, cyano, NR''R''', -COR'', -COOR'', -
CONR''R''', aryl, -alkylaryl;

R represents a lower alkyl or H;

R' represents H, lower alkyl, alkoxyalkyl or alkoxycarbonyl;

R'', R''' identical or different independently represent H or alkyl;

15 HET representing a non aromatic monocyclic heterocycle containing at least one
nitrogen atom, which is linked to R;

B represents a single bond or an -alkyl- group;

A represents O, NH or S;

20 Ar is a mono or polycyclic aromatic or a mono or polycyclic heteroaromatic which
can be optionally substituted with one or more of:

- halo; azido; cyano; hydroxy; nitro;
- alkyl; alkoxy; alkylsulfanyl; alkenyl; alkynyl; alkenyloxy; alkenyloxy;
alkenylsulfanyl; alkynylsulfanyl; cycloalkoxy; cycloalkylalkyl;

25 whose alkyl, alkenyl, alkynyl or cycloalkyl part can be substituted with one
or more of halo, hydroxy, polyhydroxy, alkoxy, hydroxyalkoxy, cyano, amino,
aminoalkyl, alkylamino, dialkylamino, aminoalkylamino, aminoalkylaminocarbonyl,
alkoxycarbonylamino, diarylmethylimino (where aryl is optionally substituted with
one or more of hydroxy or halo), cycloalkenylimino (where cylalkenyl is optionally
substituted with one or more of alkyl, OH), alkylsulfanyl, alkylsulfinyl, alkylsulfonyl,
30 cycloalkyl, polycycloalkyl, cycloalkenyl, polycycloalkenyl, guanidino,
alkylcarbonylguanidino, acylguanidino, cyanoguanidino, alkoxy carbonylguanidino,
alkoxy carbonyl, alkoxy carbonylalkylamino, alkoxy carbonylalkylcycloalkyl,

alkoxycarbonylheterocyclyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylalkoxy, aryloxy, arylsulfanyl, arylsulfinyl, arylsulfonyl, heteroaryl, heterocyclyl (heterocyclyl being optionally substituted with one or more of oxo, amino, imino), heteroaryloxy, heterocyclyloxy, heteroarylamino, heterocyclylamino, hydrazinocarbonyl, hydroxyalkylcycloalkyl, N-alkyl(thioureido), phtalimido, ureido, oxocycloalkenylamino substituted with amino, carbamimidoylheterocyclyl;

• amino; alkylamino; alkylcarbonyl; alkoxycarbonyl; alkylsulfanyl; alkylsulfinyl; alkylsulfonyl; alkylsulfonyloxy

whose alkyl can be substituted with one or more of halo;

• aminocarbonyl which can be N-substituted with one or two of alkyl, aryl, arylalkyl; • aryl; arylalkyl; aryloxy; arylalkoxy; arylalkylamino; arylalkylsulfanyl; heteroaryl; heteroaryloxy

whose (hetero)aryl part can be substituted with one or more of amino, halo, alkyl, (poly)haloalkyl, hydroxyalkyl, alkoxy, (poly)haloalkoxy, alkoxycarbonylamino, alkylcarbonyl, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, nitro, cyanoalkyl, or fused with a non aromatic heterocycle;

• heterocyclyl; heterocyclyloxy; heterocyclylalkoxy

whose heterocycle can be substituted with one or more of halogenoalkyl, acylamino, acyloxy, amino, alkyl, alkylamino, dialkylamino, aminoalkyl, oxo, carbamimidoyl, halo, hydroxy, hydroxyalkyl, hydroxymethyl, alkoxycarbonyl;

or

• fused with a non aromatic heterocycle (optionally substituted with one or more of halogens) or carbocycle;

as well as their enantiomers, diastereomers, mixtures thereof and pharmaceutically acceptable salts, tautomers, hydrates and solvates.

Unless specified otherwise, the terms used hereabove or hereafter have the meaning ascribed to them below:

“Halo” or “halogen” refers to fluorine, chlorine, bromine or iodine atom.

30

Halogenoalkyl refers to a C1-C9-alkyl moiety wherein one or more hydrogen atoms and refers in particular to perhaloalkyl.

“Perhaloalkyl” represents a C1-C9-alkyl moiety wherein all hydrogen atoms are substituted with same or different halogen atoms, for example, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CCl}_3$, $-\text{CF}_2\text{Cl}$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{CF}_2-\text{CF}_3$.

35

"Perhaloalkoxy" represents a perhaloalkyl linked via an oxygen atom, for example, $-\text{O}-\text{CF}_3$, $-\text{O}-\text{CHF}_2$, $-\text{O}-\text{CH}_2\text{CF}_3$.

"Alkyl" represents an aliphatic-hydrocarbon group which may be straight or
5 branched having 1 to 20 carbon atoms in the chain unless specified otherwise. Preferred
alkyl groups have 1 to 12 carbon atoms, more preferably have 1 to 6 carbon atoms in the
chain; lower alkyls have preferably 1 to 4 carbon atoms. Branched means that one or
more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl
chain. Exemplary alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-
10 pentyl, 3-pentyl, octyl, nonyl, decyl.

"Alkenyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon
double bond and which may be straight or branched having 2 to 15 carbon atoms in the
chain unless specified otherwise. Preferred alkenyl groups have 2 to 12 carbon atoms in
15 the chain; and more preferably about 2 to 6 carbon atoms in the chain. Exemplary alkenyl
groups include ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl,
heptenyl, octenyl, nonenyl, decenyl.

"Alkynyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon triple
20 bond and which may be straight or branched having 2 to 15 carbon atoms in the chain
unless specified otherwise. Preferred alkynyl groups have 2 to 12 carbon atoms in the
chain; and more preferably 2 to 4 carbon atoms in the chain. Exemplary alkynyl groups
include ethynyl, propynyl, n-butyne, 2-butyne, 3-methyl-1-butyne, n-pentyne,
4,4-dimethyl-2-pentyne, heptyne, octyne and decyne.

25

"Carbocycle" refers to a saturated or unsaturated non aromatic mono-
or multicyclic hydrocarbon ring system of 3 to 10 carbon atoms, preferably of 4 to 10
carbon atoms.

30 "Cycloalkyl" refers to a saturated non-aromatic mono- or multicyclic hydrocarbon
ring system of 3 to 10 carbon atoms, preferably of 4 to 10 carbon atoms. Preferred ring
sizes of rings of the ring system include 4 to 6 ring atoms. Exemplary monocyclic
cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the
like. Exemplary multicyclic cycloalkyl include 1-decalin, norbornyl, adamant-(1- or 2-)yl.

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"Aryl" refers to an aromatic monocyclic or multicyclic hydrocarbon ring system of 6 to 14 carbon atoms, preferably of 6 to 10 carbon atoms. Exemplary aryl groups include phenyl, naphthyl, indenyl, phenanthryl, biphenyl.

The terms "heterocycle" or "heterocyclic" refer to a saturated or partially unsaturated non aromatic stable 3 to 14, preferably 5 to 10-membered mono, bi or multicyclic rings wherein at least one member of the ring is a hetero atom. Typically, heteroatoms include, but are not limited to, oxygen, nitrogen, sulfur, selenium, and phosphorus atoms. Preferable heteroatoms are oxygen, nitrogen and sulfur. Preferred non aromatic heterocyclic include, but are not limited to oxetanyl, tetrahydrofuranyl, dioxolanyl, tetrahydropyranyl, dioxanyl, pyrrolidinyl, piperidyl, morpholinyl, imidazolidinyl, pyranyl. Preferred saturated heterocycles are chosen from tetrahydrofuranyl, dioxolanyl, tetrahydropyranyl, dioxanyl, pyrrolidinyl, piperidyl, morpholinyl, imidazolidinyl, more preferably tetrahydrofuranyl, dioxolanyl, tetrahydropyranyl.

The term "heteroaryl" refers to a 5 to 14, preferably 5 to 10 membered aromatic mono-, bi- or multicyclic ring wherein at least one member of the ring is a hetero atom. Examples include pyrrolyl, pyridyl, pyrazolyl, thienyl, pyrimidinyl, pyrazinyl, tetrazolyl, indolyl, quinolinyl, purinyl, imidazolyl, thienyl, thiazolyl, benzothiazolyl, furanyl, benzofuranyl, 1,2,4-thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, carbazolyl, benzimidazolyl, isoxazolyl.

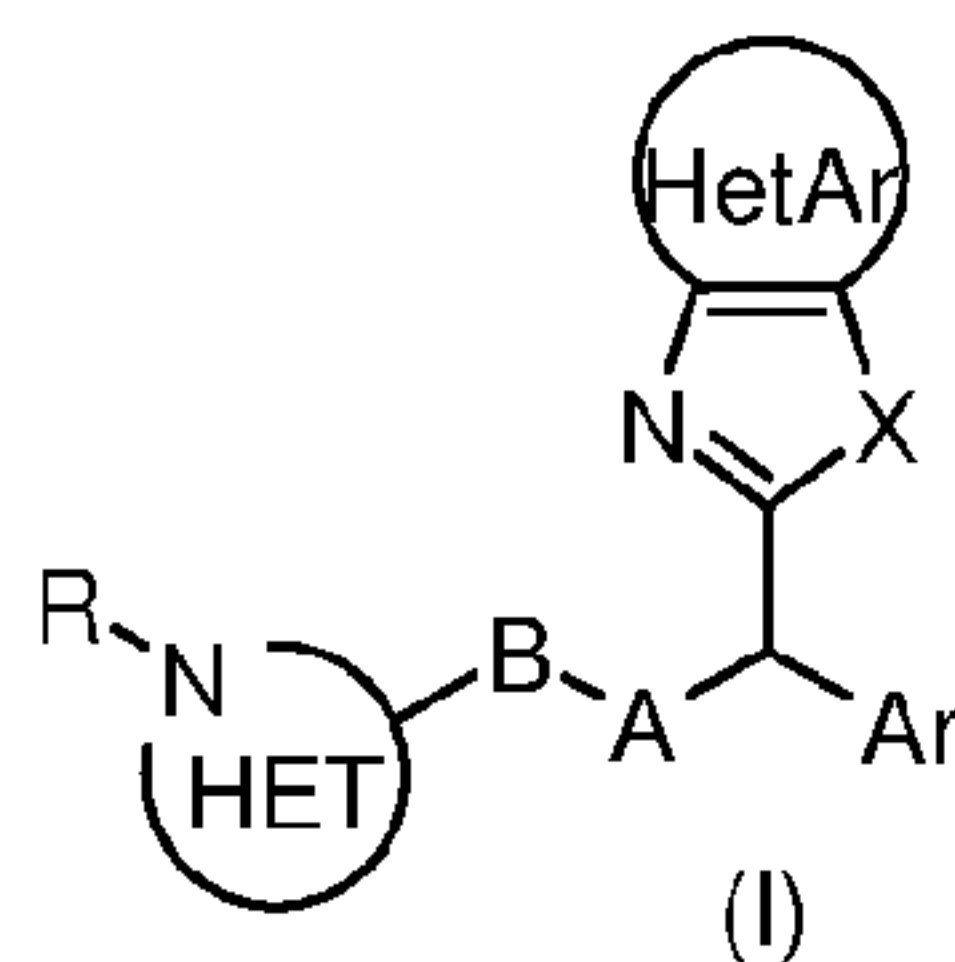
"Acyl" means an H-CO- or alkyl-CO- group wherein the alkyl group is as herein described. Preferred acyls contain a lower alkyl. Exemplary acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Alkyl", "cycloalkyl", "alkenyl", "alkynyl", "aryl", "heteroaryl", "heterocycle" also refers to the corresponding "alkylene", "cycloalkylene", "alkenylene", "alkynylene", "arylene", "heteroarylene", "heterocyclene" which are formed by the removal of two hydrogen atoms.

As used herein, "carbamimidoyl" also refers to "amidino".

A first group of compounds according to the invention may be defined as follows:

6



wherein:

X represents NR' or S;

HetAr represents a phenyl, optionally substituted with one or more substituents
5 chosen from hydrogen, halogen, amino, alkyl;

R represents H or a lower alkyl;

R' represents H, alkyl, alkoxyalkyl, alkoxycarbonyl;

HET representing a non aromatic 5 or 6 membered heterocycle containing one
nitrogen atom, which is linked to R;

10 B represents a single bond or a $-\text{CH}_2-$ group;

A represents O, NH or S;

Ar is a thienyl, phenyl or naphthyl or 5 to 6 membered heteroaromatic where the
phenyl can be optionally substituted with one or more of:

- halo; azido; cyano; hydroxy; nitro; alkyl;
- 15 • alkoxy; alkylsulfanyl; alkenyl; alkenylsulfanyl; alkynyl; alkenyloxy; alkenyloxy;
cycloalkoxy; cyloalkylalkyl

whose alkyl, alkenyl, alkynyl or or cycloalkyl part can be substituted with
one or more of halo, hydroxy, alkoxy, hydroxyalkoxy, cyano, amino, aminoalkyl,
alkylamino, aminoalkylamino, dialkylamino, aminoalkylaminocarbonyl,
20 alkoxycarbonylamino, diarylmethylimino (where aryl is optionally substituted with
one or more of hydroxy or halo), cycloalkenylimino (where cylalkenyl is optionally
substituted with one or more of alkyl, OH), alkylsulfanyl, alkylsulfonyl, cycloalkyl,
(poly)cycloalkenyl, guanidino, alkylcarbonylguanidino, acylguanidino,
alkoxycarbonylguanidino, alkoxycarbonyl, alkoxycarbonylalkylamino, alkoxy-
25 carbonylheterocyclyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl,
alkylcarbonylalkoxy, aryloxy, arylsulfonyl, heteroaryl, heterocyclyl (heterocyclyl
being optionally substituted with one or more of oxo, amino, imino),
heterocyclylamino, hydrazinocarbonyl, N-alkyl(thioureido), phtalimido, ureido,
oxocycloalkenylamino substituted with amino, carbamimidoylheterocyclyl;

- 30 • amino; alkylamino; alkylcarbonyl; alkoxycarbonyl; alkylsulfanyl; alkylsulfonyl;
alkylsulfonyloxy

whose alkyl can be substituted with one or more of halo;

- aminocarbonyl which can be N-substituted with one or two of alkyl, aryl, arylalkyl;
- aryl; arylalkyl; aryloxy; arylalkoxy; arylalkylsulfanyl; heteroaryl; heteroaryloxy

whose (hetero)aryl part can be substituted with one or more of amino, halo, alkyl, (poly)haloalkyl, hydroxyalkyl, alkoxy, (poly)haloalkoxy, alkoxycarbonylamino, alkylcarbonyl, alkylsulfanyl, nitro, cyanoalkyl, or is fused with a non aromatic heterocycle;

- heterocyclyloxy; heterocyclylalkoxy; heterocyclyl

whose heterocycle can be substituted with one or more of halo, halogenoalkyl, acylamino, acyloxy, amino, alkyl, alkylamino, dialkylamino, aminoalkyl, oxo, carbamimidoyl, hydroxy, hydroxyalkyl;

or

- fused with a non aromatic heterocycle (optionally substituted with one or more of halogens) or carbocycle;

as well as their enantiomers, diastereomers, mixtures thereof and pharmaceutically acceptable salts, tautomers, hydrates and solvates.

Further group of compounds are those of formula (I) where:

X represents NH or S; and/or

HetAr represents a phenyl; and/or

R represents methyl; and/or

HET represents a piperidine or pyrrolidine; and/or

HET represents a piperidine; and/or

B represents a single bond; and/or

A represents O or NH;

Ar is a phenyl which can be optionally substituted with one or more of:

- halo; azido; cyano; hydroxy; nitro; alkyl;
- alkoxy; alkylsulfanyl; alkenyl; alkynyl; alkenyloxy; alkenyloxy;

whose alkyl; alkenyl or alkynyl part can be substituted with one or more of halo, hydroxy, alkoxy, hydroxyalkoxy, cyano, amino, alkylamino, aminoalkylamino, alkylsulfanyl, alkylsulfonyl, cycloalkyl, (poly)cycloalkenyl, guanidino, acylguanidino, alkoxycarbonylguanidino, alkoxycarbonyl, alkoxycarbonylalkylamino, alkoxy-carbonylheterocyclyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylalkoxy, aryloxy, arylsulfonyl, heteroaryl, heterocyclyl, heterocyclylamino, hydrazinocarbonyl, N-alkyl(thioureido), phtalimido, ureido, oxocycloalkenylamino substituted with amino, carbamimidoylheterocyclyl;

• amino; alkylamino; alkylcarbonyl; alkoxy carbonyl; alkylsulfanyl; alkylsulfonyl; alkylsulfonyloxy

whose alkyl can be substituted with one or more of halo;

• aminocarbonyl which can be N-substituted with one or two of alkyl, aryl, arylalkyl;

5 • aryl; aryloxy; arylalkoxy; arylalkylsulfanyl; heteroaryl

whose aryl part can be substituted with one or more of amino, halo, alkyl, (poly)haloalkyl, hydroxyalkyl, alkoxy, (poly)haloalkoxy, alkoxy carbonylamino, alkylcarbonyl, alkylsulfanyl, nitro, cyanoalkyl, or is fused with a non aromatic heterocycle;

10 • heterocyclyloxy; heterocyclylalkoxy

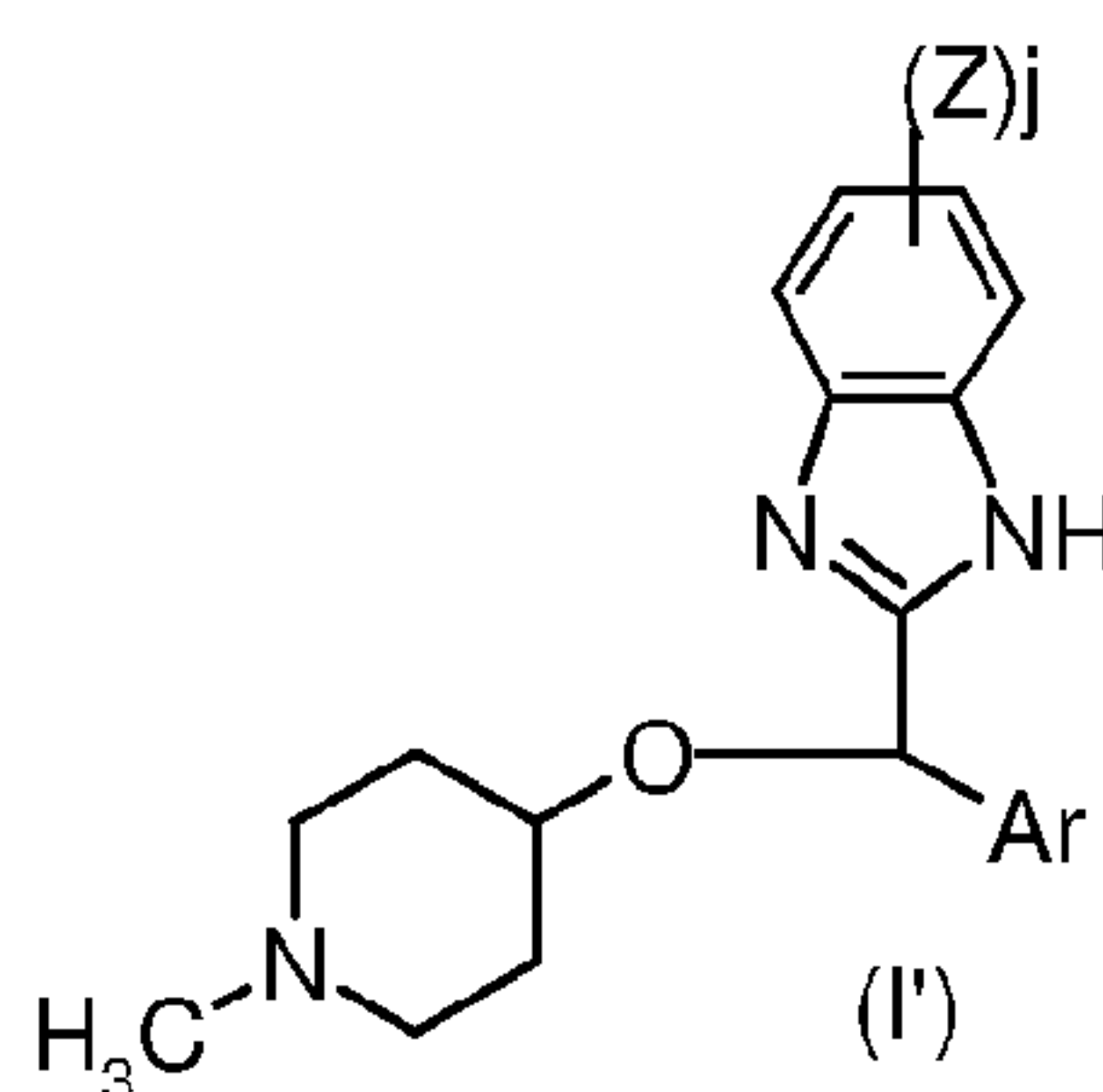
whose heterocycle can be substituted with one or more of acylamino, acyloxy, amino, alkyl, carbamimidoyl, hydroxy, hydroxyalkyl;

or

• fused with a non aromatic heterocycle;

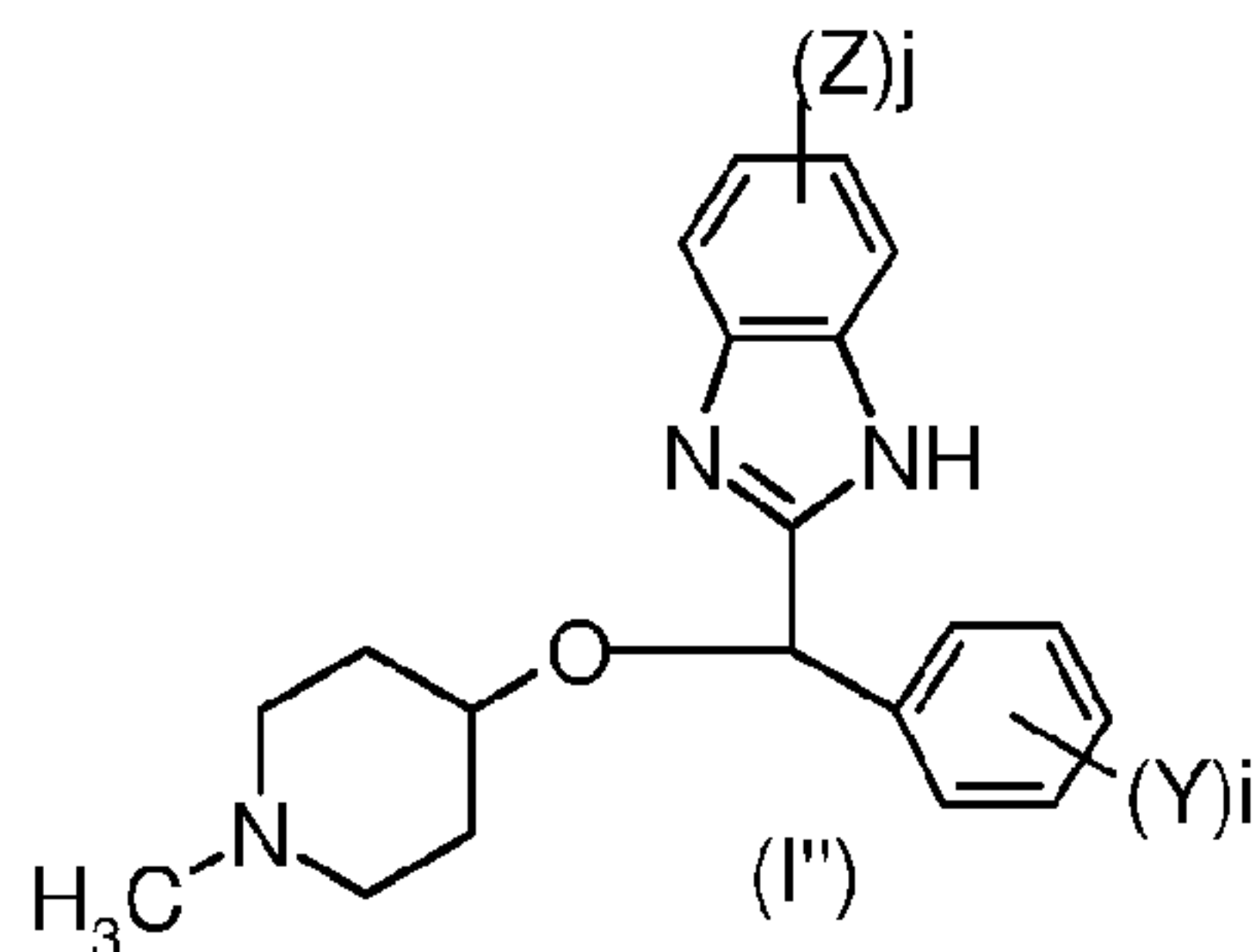
15 as well as their enantiomers, diastereomers, mixtures thereof and pharmaceutically acceptable salts, tautomers, hydrates and solvates.

In particular, the compounds of formula (I) may be chosen from those of formula (I') below:



20

and (I'') below:



where

25 Ar is defined as above; and/or

i is 0, 1, 2, or 3; and/or

j is 0, 1, 2, or 3; and/or

Y is chosen from halo, hydroxy, alkyl, perhalogenoalkyl, alkoxy; and/or

Z is chosen from halo, hydroxy, alkyl, alkoxy.

5

More particularly, in formula (I') and (I''):

i is 1, 2 or 3 and Y is chosen from halo, hydroxy, alkyl, perhalogenoalkyl, alkoxy;
and/or

j is 0.

10

In one preferred embodiment, the present invention provides a compound selected from the group consisting of:

- 2-[(1-methylpiperidin-4-yloxy)phenylmethyl]benzothiazole
- 2-[(1-methylpyrrolidin-3-yloxy)phenylmethyl]benzothiazole
- 15 - 2-[(4-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(4-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-fluorophenyl)(1-methylpiperidin-4-yloxymethyl]benzothiazole
- 2-[(2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)-p-tolylmethyl]benzothiazole
- 20 - 2-[(1-methylpiperidin-4-yloxy)(m-tolyl)methyl]benzothiazole
- (benzothiazol-2-yl-phenylmethyl)(1-methylpiperidin-4-yl)amine
- 2-[(2,3-dihydrobenzo[1,4]dioxin-6-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 25 - 2-[(2,4-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)thiophen-2-ylmethyl]benzothiazole
- 2-[(4-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3,5-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)thiophen-3-ylmethyl]benzothiazole
- 30 - 2-[(1-methylpiperidin-4-yloxy)naphthalen-1-ylmethyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)naphthalen-2-ylmethyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(5-methylthiophen-2-yl)methyl]benzothiazole
- 2-[benzo[1,3]dioxol-5-yl(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [(benzothiazol-2-yl)(m-tolyl)methyl](1-methylpiperidin-4-yl)amine
- 35 - 2-[(3-allyloxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethoxyphenyl)methyl]benzothiazole

- 2-[(1-methylpiperidin-4-yloxy)(4-trifluoromethoxyphenyl)methyl]benzothiazole
- [benzothiazol-2-yl(3-methoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(1-methylpiperidin-4-yloxy)(3-propoxy-phenyl)methyl]benzothiazole
- 2-[(3-bromo-phenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 5 - 2-[(1-methylpiperidin-4-yloxy)(3-phenoxy-phenyl)methyl]benzothiazole
- 5-methyl-2-[(1-methylpiperidin-4-yloxy)phenylmethyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)phenylmethyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethylphenyl)methyl]benzothiazole
- 2-[(2,3-dihydrobenzofuran-5-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 10 - 5-fluoro-2-[(1-methylpiperidin-4-yloxy)phenylmethyl]benzothiazole
- 2-[(4-fluoro-3-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [benzothiazol-2-yl(4-fluoro-3-methyl-phenyl)methyl](1-methylpiperidin-4-yl)amine
- (benzothiazol-2-yl-*p*-tolylmethyl)(1-methylpiperidin-4-yl)amine
- [(benzofuran-2-yl)(benzothiazol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- 15 - 2-[(3-fluoro-5-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [(1*H*-benzimidazol-2-yl)phenylmethyl](1-methylpiperidin-4-yl)amine
- 2-[(3-fluoro-5-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 20 - [benzothiazol-2-yl(3-fluoro-5-methoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [benzothiazol-2-yl(3-fluoro-5-methylphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(3-benzyloxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[benzofuran-5-yl(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-ethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 25 - [benzothiazol-2-yl(3-iodophenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(1-methylpiperidin-4-yloxy)(3-propoxyphenyl)methyl]-1*H*-benzimidazole
- [(1*H*-benzimidazol-2-yl)(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- (benzothiazol-2-ylpyridin-3-ylmethyl)(1-methylpiperidin-4-yl)amine
- 30 - 2-[biphenyl-3-yl(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- {3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxymethyl)biphenyl-3-yl}methanol
- 2-[(3-isopropoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 35 - [benzothiazol-2-yl(1*H*-pyrrol-2-yl)methyl](1-methylpiperidin-4-yl)amine

- [(1*H*-benzimidazol-2-yl)(3-trifluoromethylphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-trifluoromethoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 5 - [(1*H*-benzimidazol-2-yl)(3-ethylphenyl)methyl](1-methylpiperidin-4-yl)amine
- 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenol
- 2-[(1-methylpiperidin-4-yloxy)(3-pyridin-3-ylphenyl)methyl]benzothiazole
- [(1*H*-benzimidazol-2-yl)(3-bromophenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-benzyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 10 - [(1*H*-benzimidazol-2-yl)(3-isopropylphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-isobutoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(3-methylbutoxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-butoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 15 - [(1*H*-benzimidazol-2-yl)(3-methoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- trifluoromethanesulfonic acid 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl ester
- trifluoromethanesulfonic acid 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl ester
- 20 - [(1*H*-benzimidazol-2-yl)(3-cyclohexylmethoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-fluorophenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-methylsulfanylphenyl)methyl](1-methylpiperidin-4-yl)amine
- 25 - [(1*H*-benzimidazol-2-yl)(3-hexylphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-isopropoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-ylamine
- 2-[(3-butylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 30 - 2-[biphenyl-3-yl(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- [benzothiazol-2-yl(3-bromophenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-ethoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(*m*-tolyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-phenoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 35 - {3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-yl}methanol

- 3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-ylamine
- [benzothiazol-2-yl(3-isopropoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(1-methylpiperidin-4-yloxy)(3-pyridin-3-ylphenyl)methyl]-1*H*-benzimidazole
- 1-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-ylamino)methyl]phenyl}ethanone
- 5 - [benzothiazol-2-yl(3-butoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(3-butoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [benzothiazol-2-yl(3-cyclohexylmethoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)biphenyl-3-ylmethyl](1-methylpiperidin-4-yl)amine
- 10 - [(1*H*-benzimidazol-2-yl)(3-pentyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(2'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(3'-nitrobiphenyl-3-yl)methyl]benzothiazole
- {3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-yl}acetonitrile
- 2-[(3'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 15 - 2-[(4'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [benzothiazol-2-yl(3-benzyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- (benzothiazol-2-ylbiphenyl-3-ylmethyl)(1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(4-fluorobenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 20 - [(1*H*-benzimidazol-2-yl)(3-benzylsulfanylphenyl)methyl](1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(3-fluorobenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(2-phenoxyethoxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 25 - [benzothiazol-2-yl(3-benzylsulfanylphenyl)methyl](1-methylpiperidin-4-yl)amine
- 1-{3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-yl}ethanone
- 2-[(3'-fluoro-biphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 30 - 1-{3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-yl}ethanone
- [benzothiazol-2-yl(3-methylsulfanylphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(3-allyloxyphenyl)(1*H*-benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(2-fluorobenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 35

- 2-[(1-methylpiperidin-4-yloxy)(2'-methylsulfanylbiphenyl-3-yl)methyl]-1*H*-benzimidazole
- 2-[(4'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)(3'-methylsulfanylbiphenyl-3-yl)methyl]-1*H*-benzimidazole
- 5 - 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(4'-trifluoromethylbiphenyl-3-yl)methyl]-1*H*-benzimidazole
- 10 - {(1*H*-benzimidazol-2-yl)[3-(tetrahydropyran-2-yloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 2-[(2'-chlorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(3',4'-dichlorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- {3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-2-yl}methanol
- 15 - {(1*H*-benzimidazol-2-yl)[3-(4-methoxybenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(3-methoxybenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 20 - 3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-ylamino)methyl]phenol
- {3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-2-yl}methanol
- 2-[(1-methylpiperidin-4-yloxy)(3'-methylsulfanylbiphenyl-3-yl)methyl]benzothiazole
- {(1*H*-benzimidazol-2-yl)[3-(2-methylbenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 25 - {(1*H*-benzimidazol-2-yl)[3-(4-methylbenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-nitrophenyl)methyl](1-methylpiperidin-4-yl)amine
- [(3-azidophenyl)(1*H*-benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(3',4'-dichlorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 30 - {(1*H*-benzimidazol-2-yl)[3-(2-ethoxyethoxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-pent-4-enyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(4'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 35 - 2-[(2'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole

- {3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-yl}carbamic acid *tert*-butyl ester
- 2-[(3'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(4'-trifluoromethylbiphenyl-3-yl)methyl]benzothiazole
- 5 - 2-[(1-methylpiperidin-4-yloxy)(2',3',4'-trifluorobiphenyl-3-yl)methyl]benzothiazole
- 2-[(2'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- {3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-yl}carbamic acid *tert*-butyl ester
- [(1*H*-benzimidazol-2-yl)(3-furan-2-ylphenyl)methyl](1-methylpiperidin-4-yl)amine
- 10 - [(1*H*-benzimidazol-2-yl)(3-but-3-enyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(4-methylpentyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 2-[(1-methylpiperidin-4-yloxy)(3-pyrazol-1-ylphenyl)methyl]benzothiazole
- 15 - 2-[(3-benzylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- {(1*H*-benzimidazol-2-yl)[3-(2,5-difluoro-benzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 2-[(3-benzylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(2-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 20 - 2-[(3-ethylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-ethylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- {3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid methyl ester
- 2-[(3-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 25 - 2-[[3-(2,5-difluorobenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
- 30 - 2-[(3-ethylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid methyl ester
- 2-[[3-(2,3-difluorobenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 35 - {(1*H*-benzimidazol-2-yl)[3-(2,3-difluoro-benzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine

- 2-[[3-(2-fluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(m-tolyl)methyl]-1*H*-benzimidazole
- 5,6-dichloro-2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-1*H*-benzimidazole
- 5-fluoro-2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-1*H*-benzimidazole
- 5 - 2-[(2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)(3-pent-4-enyloxy-phenyl)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(4,4,4-trifluoro-butoxy)phenyl]methyl]benzothiazole
- 5-bromo-2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-1*H*-benzimidazole
- 2-[[3-(3-fluorobenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 10 - 3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzonitrile
- 2-[[3-(furan-2-yl)methylsulfanyl]phenyl](1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- ((1*H*-benzimidazol-2-yl)-{3-[3-(2-methyl-[1,3]dioxolan-2-yl)-propoxy]phenyl}methyl)(1-methylpiperidin-4-yl)amine
- 15 - {(1*H*-benzimidazol-2-yl)[3-(4,4,4-trifluoro-butoxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 2-[[3-(3-fluoropropoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)-p-tolyl-methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(3,3,3-trifluoro-propoxy)phenyl]methyl]benzothiazole
- 20 - 2-[(4-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- {(1*H*-benzimidazol-2-yl)[3-(2-fluoro-ethoxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- ((1*H*-benzimidazol-2-yl)-{3-[2-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)ethoxy]phenyl}methyl)(1-methylpiperidin-4-yl)amine
- 25 - 2-[(1-methylpiperidin-4-yloxy)(4'-trifluoromethoxy-biphenyl-3-yl)methyl]-1*H*-benzimidazole
- 2-[(4'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(3-benzo[1,3]dioxol-5-yl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 30 - 2-[[3-(3-methoxybenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentan-2-one
- 2-[(1-methylpiperidin-4-yloxy)[3-(3-trifluoromethyl-benzyloxy)phenyl]methyl]benzothiazole
- 35 - 4-[benzothiazol-2-yl(3-bromo-phenyl)methoxy]-1,1-dimethylpiperidinium

- 2-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)isoindole-1,3-dione
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-yn-1-ol
- 5 - 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-yn-1-ol
- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-yn-1-ol
- 2-[(1-methylpiperidin-4-yloxy)-o-tolyl-methyl]-1*H*-benzimidazole
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynylamine
- 10 - 2-[(3-ethynylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(3-nitro-benzyloxy)phenyl]methyl]benzothiazole
- 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzonitrile
- 2-[(1-methylpiperidin-4-yloxy)[3-(1*H*-[1,2,3]triazol-4-yl)phenyl]methyl]-1*H*-benzimidazole
- 15 - 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzoic acid methyl ester
- 2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-3*H*-benzimidazol-4-ylamine
- 2-[(1-methylpiperidin-4-yloxy)(3-methylsulfanyl-phenyl)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(3-methylsulfanyl-phenyl)methyl]-1*H*-benzimidazole
- 20 - 2-[(3-methanesulfonylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(4-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}acrylic acid *tert*-butyl ester
- 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzoic acid ethyl ester
- 25 - {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}methanol
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}propionic acid *tert*-butyl ester
- 2-[[3-(2-benzenesulfonylvinyl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 30 - 2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-3*H*-benzimidazol-4-ol
- [benzothiazol-2-yl(4'-methoxy-biphenyl-3-yl)methyl](1-methylpiperidin-4-yl)amine
- 2-[[3-(2-methanesulfonylvinyl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(2-chloro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 35 - 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrimidin-2-ol
- 2-[(3-*tert*-butylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

- 2-[(1-methylpiperidin-4-yloxy)(3-pyrimidin-5-yl-phenyl)methyl]benzothiazole
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}acrylonitrile
- 2-[(1-methylpiperidin-4-yloxy)(3-vinyl-phenyl)methyl]benzothiazole
- 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]-*N*-benzyl-*N*-
- 5 methylbenzamide
- 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]-*N*-propylbenzamide
- 2-[(2,4-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 *H*-benzimidazole
- [(1 *H*-benzimidazol-2-yl)(4'-methoxy-biphenyl-3-yl)methyl](1-methylpiperidin-4-yl)amine
- 10 - 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]-*N*-methyl-*N*-phenylbenzamide
- 3-[(1 *H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylamine
- 2-[(3-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 *H*-benzimidazole
- 2-[(4-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 *H*-benzimidazole
- 15 - 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-yn-1-ol
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy)methyl}-phenylamine
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
- 20 - 2-[(3-azidophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 *H*-benzimidazole
- 2-{(1-methylpiperidin-4-yloxy)[3-(2-pyrazin-2-yl-ethylsulfanyl)phenyl]methyl}-1 *H*-benzimidazole
- 2-{(1-methylpiperidin-4-yloxy)[3-(2-pyrazin-2-yl-ethylsulfanyl)phenyl]methyl}benzothiazole
- 25 - {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}benzyl-amine
- 3-{3-[(1 *H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-3-methyl-butan-1-ol
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-yn-1-ol
- 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-yn-1-ol
- 30 - 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}butan-1-ol
- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-cyclopropyl)acetic acid methyl ester
- 2-{(1-methylpiperidin-4-yloxy)[3-(2-[1,2,3]triazol-2-yl-ethylsulfanyl)phenyl]methyl}benzothiazole
- 35 - 2-{(1-methylpiperidin-4-yloxy)[3-(2-[1,2,3]triazol-1-yl-ethylsulfanyl)phenyl]methyl}benzothiazole

- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-3-methylbutan-1-ol
- 2-[(1-methylpiperidin-4-yloxy)(3-morpholin-4-yl-phenyl)methyl]benzothiazole
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethanol
- 5 - 2-[(1-methylpiperidin-4-yloxy)(3-vinyl-phenyl)methyl]-1 *H*-benzimidazole
- 3-{3-[(1 *H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-1-ol
- 1-{3-[(1 *H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-2-ol
- 10 - 4-{3-[(1 *H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol
- 2-{3-[(1 *H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine
- 2-[(1-methylpiperidin-4-yloxy)[3-(2-methylsulfanyl-ethoxy)phenyl]methyl}benzothiazole
- 15 - 2-[(1-methylpiperidin-4-yloxy)(2-trifluoromethoxy-phenyl)methyl]-1 *H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)-*p*-tolylmethyl]-1 *H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)-*p*-tolyl-methyl]-1 *H*-benzimidazole
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-1-ol
- 20 - 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-2-ol
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol
- 2-(1-{3-[(1 *H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-cyclopropyl)ethanol
- 25 - 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}propan-1-ol
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-*N*-methylacetamide
- 2-[(1-methylpiperidin-4-yloxy)[3-(2*H*-pyrazol-3-yl)phenyl]methyl}benzothiazole
- 30 - 2-[(3-bromo-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1 *H*-benzimidazole
- 2-[(2-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 *H*-benzimidazole
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetamide
- {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid hydrazide
- 35 - 2-[(1-methylpiperidin-4-yloxy)[3-(pyridin-4-ylmethoxy)phenyl]methyl}benzothiazole
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}butan-1-ol

- 2-[[3-(furan-2-ylmethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-(1-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-cyclopropyl)ethanol
- 2-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine
- 5 - 1-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]benzyloxy}propan-2-one
- 2-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamine
- 2-[(1-methylpyrrolidin-3-yloxy)phenyl-methyl]-1*H*-benzimidazole
- [(1*H*-benzimidazol-2-yl)-p-tolyl-methyl](1-methylpiperidin-4-yl)amine
- 2-[(3-ethylsulfanyl-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-
- 10 benzimidazole
- 1-(3-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyloxy)-propan-2-one
- 1-(3-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyloxy)-propan-2-ol
- 15 - 2-[[3-(2-methoxyethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- *N*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine
- (2-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)methylamine
- 20 - 2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethoxy-phenyl)methyl]-1*H*-benzimidazole
- 2-[(2-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 4-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynylamine
- 2-{(1-methylpiperidin-4-yloxy)[3-(pyridin-2-ylmethoxy)phenyl]methyl}benzothiazole
- 2-{(1-methylpiperidin-4-yloxy)[3-(pyridin-3-ylmethoxy)phenyl]methyl}benzothiazole
- 25 - 2-[(3-Cyclohexylmethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynylamine
- 5-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propane-1,2-diol
- 30 - 5-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenyl}pentylamine
- 2-{3-[benzothiazol-2-yl](1-ethyl-piperidin-4-yloxy)methyl]phenoxy}ethylamine
- 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamine
- 6-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexan-1-ol
- 35 - 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}butylamine

- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine
- 6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexan-1-ol
- 5 - 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynylamine
- 2-[benzo[1,3]dioxol-5-yl(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- (2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-urea
- (2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)(4,5-dihydro-thiazol-2-yl)amine
- 10 - 2-[(2,3-dihydrobenzo[1,4]dioxin-6-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}butylamine
- *N*-(2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine
- 15 - 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propylamine
- *N-tert*-butoxycarbonyl-*N*-(2-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine
- 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}pentylamine
- 20 - 2-[(3-[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]phenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- *N-tert*-butoxycarbonyl-*N'*-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine
- 25 - *N*-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}butyl)guanidine
- *N-tert*-butoxycarbonyl-*N'*-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}butyl)guanidine
- 2-[(1-methylpiperidin-4-yloxy)[3-(pyridin-2-ylmethoxy)phenyl]methyl]-1*H*-benzimidazole
- 30 - 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}propylamine
- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pentylamine
- *N-tert*-butoxycarbonyl-*N'*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propyl)guanidine
- 35 - 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propylamine

- 2-((1-methylpiperidin-4-yloxy)[3-(4-[1,2,3]triazol-2-yl-butoxy)phenyl]methyl)benzothiazole
- 2-((1-methylpiperidin-4-yloxy)[3-(4-[1,2,4]triazol-1-yl-butoxy)phenyl]methyl)benzothiazole
- 5 - (2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)(4,5-dihydro-1*H*-imidazol-2-yl)amine
- *N*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-*N'*-cyanoguanidine
- 6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine
- 10 - *N*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propyl)guanidine
- *N*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propyl)guanidine
- 2-((1-methylpiperidin-4-yloxy)[3-(4-morpholin-4-yl-butoxy)phenyl]methyl)benzothiazole
- 15 - (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-2-yl)methanol
- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-2-yl)methanol
- 20 - 6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hexylamine
- 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}propylamine
- 25 - 4-(2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)piperazine-1-carboxylic acid *tert*-butyl ester
- 4-(2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)piperazine-1-carboxylic acid *tert*-butyl ester
- 2-((1-methylpiperidin-4-yloxy)[3-(2-piperazin-1-yl-ethoxy)phenyl]methyl)benzothiazole
- 30 - 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}butylamine
- 2-((1-methylpiperidin-4-yloxy)[3-(4-morpholin-4-yl-butoxy)phenyl]methyl)-1*H*-benzimidazole
- 2-((1-methylpiperidin-4-yloxy)[3-(4-piperidin-1-yl-butoxy)phenyl]methyl)-1*H*-benzimidazole
- 35 - 2-[(2-fluoro-3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

- *N-tert*-butoxycarbonyl-*N*-(3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl)pentyl)guanidine
- *N-tert*-butoxycarbonyl-*N*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)guanidine
- 5 - 6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine
- 2-[(1-methylpiperidin-4-yloxy)[3-(1,2,3,6-tetrahydro-pyridin-4-yl)phenyl]methyl]-1*H*-benzimidazole
- *N-tert*-butoxycarbonyl-*N*-(5-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-5-ynyl)guanidine
- 10 - *N*-(5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)guanidine
- *N-tert*-butoxycarbonyl-*N*-(6-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine
- 15 - *N*-(6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine
- 4-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}butyl)piperazine-1-carboxylic acid *tert*-butyl ester
- 6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hexylamine
- 20 - *N-tert*-butoxycarbonyl-*N*-(6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine
- *N*-(6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine
- 1-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-3-isopropyl-thiourea
- 25 - 2-[(1-methylpiperidin-4-yloxy)[3-(3-[1,2,4]triazol-1-yl-propoxy)phenyl]methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(3-[1,2,3]triazol-2-yl-propoxy)phenyl]methyl]benzothiazole
- 30 - 2-[(1-methylpiperidin-4-yloxy)[3-(3-morpholin-4-yl-propoxy)phenyl]methyl]benzothiazole
- 4-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}propyl)piperazine-1-carboxylic acid *tert*-butyl ester
- 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-phenylsulfanyl}ethylamine
- 35

- 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}-3,6-dihydro-2*H*-pyridine-1-carboxamide
- 2-[[3-(2-chloroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- *N*-(6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hexyl)guanidine
- 2-[(1-methylpiperidin-4-yloxy)[3-(2-piperidin-1-yl-ethoxy)phenyl]methyl]-1*H*-benzimidazole
- *N*-*tert*-butoxycarbonyl-*N*-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)guanidine
- *N*-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)guanidine
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine
- 4-{3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}propyl)piperazine-1-carboxylic acid *tert*-butyl ester
- (2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamino)acetic acid *tert*-butyl ester
- 4-(5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentyl)piperazine-1-carboxylic acid *tert*-butyl ester
- *N*-(6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hexyl)guanidine
- *N*-*tert*-butoxycarbonyl-*N*-(6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hexyl)guanidine
- *N*-(5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pentyl)guanidine
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}butylamine
- [[3-(4-aminobutoxy)phenyl](1*H*-benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propylamine
- 4-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)piperazine-1-carboxylic acid *tert*-butyl ester
- (2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamino)acetic acid *tert*-butyl ester
- 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentylamine
- *N*-(4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine

- *N*-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)guanidine
- *N*-(4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}butyl)guanidine
- (5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentylamino)acetic acid *tert*-butyl ester
- 5 - 2-[(1-methylpiperidin-4-yloxy)(3-piperidin-4-ylethynyl-phenyl)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(piperidin-4-ylmethoxy)phenyl]methyl]benzothiazole
- 10 - 2-[(1-methylpiperidin-4-yloxy)[3-(piperidin-3-ylmethoxy)phenyl]methyl]benzothiazole
- 2-[[3-(1-methylpiperidin-3-ylmethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(3-piperidin-3-ylethynyl-phenyl)methyl]-1*H*-benzimidazole
- 15 - 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}pentylamine
- 2-[(1-methylpiperidin-4-yloxy)[3-(pyrrolidin-3-yloxy)phenyl]methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(pyrrolidin-3-yloxy)phenyl]methyl]benzothiazole
- 20 - 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-en-1-ol
- 3-amino-4-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamino)-cyclobut-3-ene-1,2-dione
- [[3-(6-aminohept-1-ynyl)phenyl](1*H*-benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- 25 - {[3-(4-aminobutoxy)phenyl]benzothiazol-2-yl-methyl}(1-methylpiperidin-4-yl)amine
- 2-[(3-azetidin-3-ylethynylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-en-1-ol
- 30 - 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-en-1-ol
- 4-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentyl)piperazine-1-carboxylic acid *tert*-butyl ester
- 2-[[3-(2-azetidin-3-ylethyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 35 - *N*-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine

- 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidine-1-carboxamide
- 2-[(1-methylpiperidin-4-yloxy)[3-(2-piperidin-2-yl-ethylsulfanyl)phenyl]methyl]-1*H*-benzimidazole
- 5 - 2-[(1-methylpiperidin-4-yloxy)[3-(2-piperidin-4-yl-ethyl)phenyl]methyl]-1*H*-benzimidazole
- *N*-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pentyl)guanidine
- 2-[(3-{3-(3*H*-imidazol-4-yl)propylsulfanyl]phenyl}(1-methylpiperidin-4-yloxy)methyl]-10 1*H*-benzimidazole
- *N*-*tert*-butoxycarbonyl-*N*-(4-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine
- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentylamine
- 15 - *N*-acetyl-*N'*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine
- 2-[[3-(azetidin-3-yloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}azetidin-3-ol
- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)methanol
- 20 - 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-ylamine
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ol
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ol
- *N*-(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)acetamide
- 25 - 2-[[3-(5-imidazol-1-ylpent-1-ynyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(5-pyrazol-1-yl-pent-1-ynyl)phenyl]methyl]-1*H*-benzimidazole
- 30 - 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-ol
- 2-[(3-[2-(1*H*-imidazol-4-yl)ethyl]phenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- acetic acid 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-yl ester
- 35 - 2-[(3-bromo-phenyl)(1-methyl-pyrrolidin-3-ylmethoxy)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(piperidin-4-yloxy)phenyl]methyl]benzothiazole

- 2-((1-methylpiperidin-4-yloxy)[3-(5-[1,2,3]triazol-2-yl-pent-1-ynyl)phenyl]methyl)-1*H*-benzimidazole
- 2-((1-methylpiperidin-4-yloxy)[3-(5-[1,2,3]triazol-1-yl-pent-1-ynyl)phenyl]methyl)-1*H*-benzimidazole
- 5 - *N*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)guanidine
- *N*1-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentyl)butane-1,4-diamine
- {[3-(6-aminohex-1-ynyl)phenyl]benzothiazol-2-yl-methyl}(1-methylpiperidin-4-yl)amine
- 10 - 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-enylamine
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}but-2-en-1-ol
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ylamine
- 15 - 2-[(2,5-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(2-fluoro-5-iodo-phenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylethynyl}azetidine-1-carboxamide
- 20 - 4-{3-[(5-fluoro-1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol
- 2-{3-[(5-fluoro-1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ylamine
- 25 - 2-[[3-(3-fluoropyrrolidin-1-yl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}but-2-enylamine
- 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 30 - 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole (enantiomer A)
- 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole (enantiomer B)
- 35 - *N*-(2-aminoethyl)-2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetamide

- N-(2-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine
- 2-(5-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)isoindole-1,3-dione
- 5 - 6-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine oxalate
- 4-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine oxalate
- N-(3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propyl)guanidine, dihydrochloride
- 10 - 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-one, oxalate
- N-(4-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butyl)guanidine, dihydrochloride
- 15 - 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}pentan-1-ol
- N-(2-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-N-(2,2-dimethylpropionyl)guanidine
- 2-[(1-methylpiperidin-4-yloxy)(4-nitrophenyl)methyl]-1H-benzimidazole
- 20 - 2-[(1-methylpiperidin-4-yloxy)[3-(pyridin-3-yloxy)phenyl]methyl]benzothiazole, oxalate
- 2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]-5-fluoro-1H-benzimidazole, oxalate
- 4-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]aniline
- 25 - 4-[(1H-benzimidazol-2-yl)(piperidin-4-yloxy)methyl]aniline, hydrochloride
- N-(2-amino-ethyl)-2-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetamide
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}-3-trifluoromethylpyrrolidin-3-ol, oxalate
- 30 - 2-[[3-(4,5-dihydro-1H-imidazol-2-ylmethylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[[3-(4,5-dihydro-1H-imidazol-2-ylmethylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole
- 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5,6-difluoro-1H-benzimidazole
- 35

- 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1-methyl-1H-benzimidazole, dioxalate
- 2-amino-5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-1,5-dihydroimidazol-4-one
- 5 - 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5,6,7-trifluoro-1H-benzimidazole
- 1-(2-ethoxyethyl)-2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, dioxalate
- 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzaldehyde
- 10 - 4-{3-[(1H-benzimidazol-2-yl)(1-methylazetidin-3-ylmethoxy)methyl]phenylsulfanyl}butylamine, oxalate
- 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzoxazole, oxalate
- {3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}methanol.
- 15 - dimethylsulfoxonium ylide of 3-bromophenylacetic acid methyl ester
- 2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer B
- 2-[(2,6-difluoro-3-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 20 - ethyl (6-{3-[(1-methyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)carbamate, oxalate
- 2-[(1H-indol-6-yl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 2-[benzo[b]thiophen-6-yl(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 25 - 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer B
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol
- 2-[(1H-benzimidazol-2-yl)hydroxymethyl]phenol
- 2-[(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylimino)phenylmethyl]phenol
- 30 - 5-(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylimino)-2-methylcyclopent-1-enol
- 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer B
- 35 - 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine, enantiomer A

- 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine, enantiomer B
- 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole, enantiomer A
- 5 - 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole, enantiomer B
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-methylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol enantiomer A
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol enantiomer B
- 10 - 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol enantiomer A
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol enantiomer B
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol enantiomer A
- 15 - 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol enantiomer B
- 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}pent-4-ynylamine, dioxalate
- 20 - 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}cyclopentylamine, oxalate
- 2-{[3-(3-fluoropyrrolidin-1-yl)phenyl](1-methylpiperidin-4-yloxy)methyl}benzothiazole, oxalate
- 5-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpyrrolidin-3-ylmethoxy)methyl]phenyl}pent-4-ynylamine, oxalate
- 25 - 2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]benzothiazole, oxalate (one epimer)
- 2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]benzothiazole, oxalate (50/50 mixture of two epimers)
- 30 - 2-[(1-methylpiperidin-4-yloxy)[3-(octahydrocyclopenta[c]pyrrol-5-yloxy)phenyl]methyl]benzothiazole, dioxalate
- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)methylamine, dioxalate
- 4-{3-[(5,6-difluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol
- 35

- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}octahydrocyclopenta[c]pyrrol-5-ylamine, dioxalate
- 2-{[3-(3-fluoropropoxy)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, oxalate
- 5 - 2-{[3-(2-fluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, oxalate
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}cyclohexylamine, oxalate
- 6-{3-[(1-methyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine, dioxalate
- 10 - 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-2-ylmethylamine, oxalate
- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)(methyl)amine, oxalate
- 15 - (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)(dimethyl)amine, oxalate
- 2-{[3-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2-yl)phenyl](1-methylpiperidin-4-yloxy)methyl}benzothiazole, dioxalate
- 2-[(2-fluoro-5-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 20 - 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenol, oxalate
- 2-[[2-fluoro-5-(2-fluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 25 - 2-[(2-fluoro-5-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 4-{3-[(1-methylpiperidin-4-yloxy)(5,6,7-trifluoro-1H-benzimidazol-2-yl)methyl]phenylsulfanyl}butylamine, oxalate
- 4-{3-[(5,6-difluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine, oxalate
- 30 - 6-{3-[[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine, dioxalate
- 6-{3-[[1-(2-methoxyethyl)-1H-benzimidazol-2-yl](1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine, dioxalate
- 35 - 2-{[3-(3-fluoropropylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, dioxalate

- 5-fluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 4,5,6-trifluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 5 - 5,6-difluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[[2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 10 - 2-[(2-chloro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate
- 15 - 2-[(4-chloro-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 7-fluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate
- 20 - 2-[(4-chloro-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate
- 2-[(3-ethoxy-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 25 - 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzoxazole, oxalate
- 2-[(1-methylpiperidin-4-yloxy)(4-trifluoromethylphenyl)methyl]-1H-benzimidazole
- 2-[(2-fluoro-4-trifluoromethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 30 - 2-[(2,4-dimethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(3-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[chroman-7-yl(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzoxazole, oxalate
- 35 - 2-[(3,5-bis-trifluoromethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate

- 5-fluoro-2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(2,3-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 5 - 2-[(3-chloro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- ethyl 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzimidazole-1-carboxylate, oxalate
- 2-[(3-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(5-bromo-2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 10 - 6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylamine, oxalate
- 5-{4-fluoro-3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine
- ethyl (5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}pent-4-ynyl)carbamate
- 15 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-chlorophenol
- ethyl (5-{4-fluoro-3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)carbamate
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-trifluoromethoxyphenol
- 20 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-methoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-methylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-bromophenol
- 25 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-ethoxyphenol
- 2-[(1H-indol-7-yl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,6-difluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,6-dichlorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-fluorophenol
- 30 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-fluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,5-difluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-fluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-chlorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-methylphenol
- 35 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-methylsulfanylphenol

- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-ethylsulfanylphenol
- 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-ol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-tert-butylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-propylphenol
- 5 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-methoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-fluoro-5-methylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-chlorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-fluoro-4-ethylphenol
- 10 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-benzylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-trifluoromethylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-chloro-6-fluorophenol
- 15 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-3-methylphenol
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]indan-5-ol
- 20 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-propoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(1-methyl-1-phenylethyl)phenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(2-fluoroethoxy)phenol
- 25 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(3-fluoropropoxy)phenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluoro-6-methylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-fluoro-4-methoxyphenol
- 30 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-phenoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluoro-6-methoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,5-dimethylphenol
- 35 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(3-fluoropropylsulfanyl)phenol

- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluoro-5-methylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(2-fluoroethylsulfanyl)phenol
- 5 - 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-hydroxybiphenyl
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-ethylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-trifluoromethylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-hydroxyphenol
- 10 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5,6,7,8-tetrahydro-1-naphthol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-trifluoromethoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-trifluoromethoxyphenol
- 15 - 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3,4-dimethylphenol
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-fluoro-2-methylphenol
- 20 - 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,4-difluoro-3-methylphenol
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol
- (1-{3-[benzothiazol-2-yl](1-methylpiperidin-4-yloxy)methyl}phenyl)-azetidin-3-yl)dimethylamine, oxalate
- 25 - 1-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ol, oxalate
- 2-[(1-methylpiperidin-4-yloxy)[3-(pyrrolidin-3-yloxy)phenyl]methyl]-1H-benzimidazole, dioxalate
- 2-[(5-chloro-2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 30 - 2-[(2-fluoro-5-trifluoromethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 6-{3-[(1-ethyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine, oxalate
- 35 - 2-[(2-fluoro-5-methoxyphenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]-1H-benzimidazole, oxalate

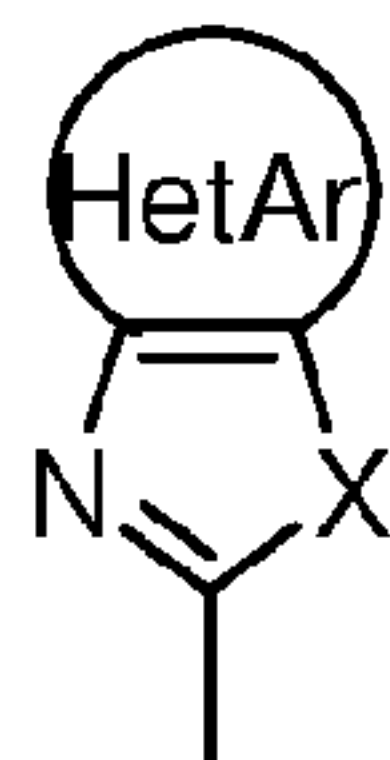
- 2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethylsulfanylphenyl)methyl]-1H-benzimidazole, oxalate
- 2-[(4-fluoro-3-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 5 - 2-[(2-fluoro-5-propoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 4-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol
- 2-{[3-(3,3-difluoropyrrolidin-1-yl)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, dioxalate
- 10 - 2-{[3-(5-fluorohexahydrocyclopenta[c]pyrrol-2-yl)phenyl](1-methylpiperidin-4-yloxy)methyl}benzothiazole, dioxalate
- 6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexylamine, oxalate
- 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}oxazolidin-2-one
- 15 - N-(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexyl)guanidine, dihydrochloride
- 4-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}but-2-enylamine
- 20 - 4-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}but-2-enylamine, oxalate
- N-(2-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-N-isobutyrylguanidine
- 3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}allylamine
- 25 - cis-2-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}cyclopropylmethylamine
- N-(3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}allyl)guanidine, trihydrochloride
- 2-[(azetidin-3-ylmethoxy)(3-bromophenyl)methyl]-1H-benzimidazole
- 30 - 2-[(3-bromophenyl)(1-methylazetidin-3-ylmethoxy)methyl]-1H-benzimidazole
- 2-[(2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(5-ethylsulfanyl-2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 35 - 2-[(azetidin-3-ylmethoxy)(2-fluoro-5-trifluoromethoxyphenyl)methyl]-1H-benzimidazole, oxalate

- 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylazetidin-3-ylmethoxy)methyl]-1H-benzimidazole, oxalate
- 2-[(3-ethylsulfanyl-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 5 - 2-[(2,2-difluorobenzo[1,3]dioxol-5-yl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(piperidin-4-yloxy)thiophen-3-ylmethyl]-1H-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)thiophen-3-ylmethyl]-1H-benzimidazole
- 2-[(piperidin-4-yloxy)thiophen-2-ylmethyl]-1H-benzimidazole
- 10 - 2-[(1-methylpiperidin-4-yloxy)thiophen-2-ylmethyl]-1H-benzimidazole

as well as their enantiomers, diastereomers, mixtures thereof and pharmaceutically acceptable salts, free forms, tautomers, hydrates and solvates.

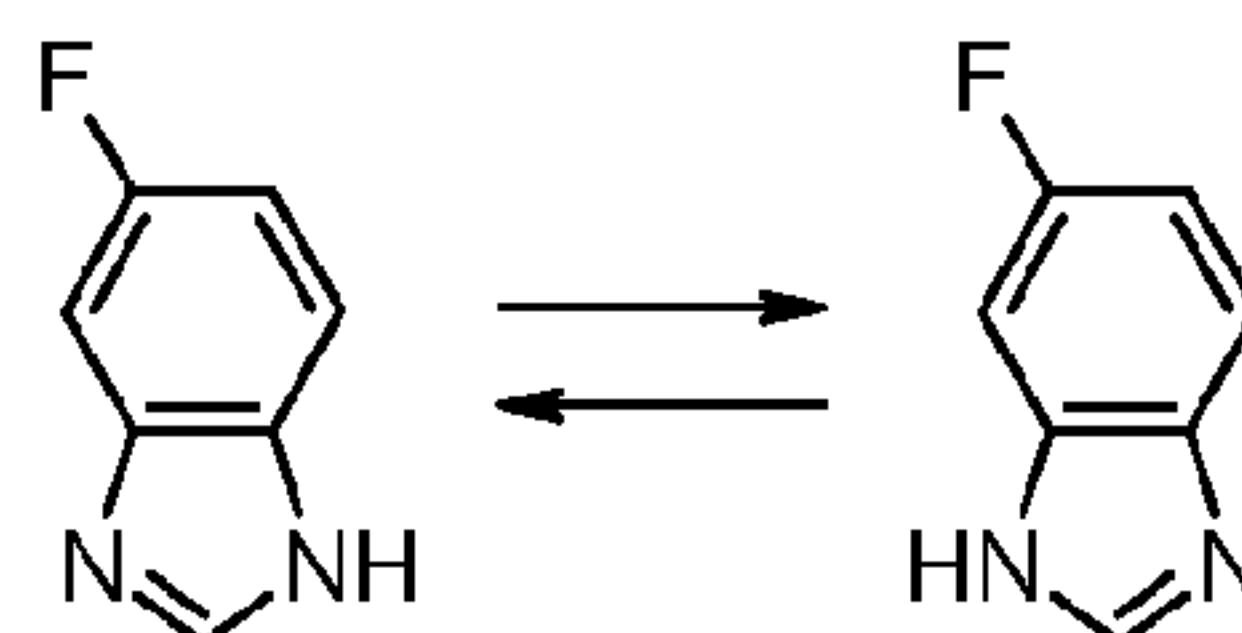
15 The compounds of formula (I) can comprise one or more asymmetric carbon atoms. They can therefore exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, as well as their mixtures, including racemic mixtures, form part of the invention.

The compounds of the invention may also comprise tautomeric forms which are all
20 encompassed by the present invention. In particular, in formula (I), the group:



may have tautomeric forms such as when HetAr is a phenyl and X is N, leading to 1*H*-benzimidazole which is a tautomer of 3*H*-benzimidazole. A representative example is illustrated below:

25



The compounds of formula (I) can be provided in the form of a free base or in the form of addition salts with acids, which also form part of the invention.

These salts are advantageously prepared with pharmaceutically acceptable acids, but salts with other acids, useful for example for the purification or for the isolation of the compounds of formula (I), also form part of the invention.

As used herein, the term "patient" refers to a warm-blooded animal such as a mammal, preferably a human or a human child, which is afflicted with, or has the potential to be afflicted with one or more diseases and conditions described herein.

As used herein, a "therapeutically effective amount" refers to an amount of a compound of the present invention which is effective in reducing, eliminating, treating or controlling the symptoms of the herein-described diseases and conditions. The term "controlling" is intended to refer to all processes wherein there may be a slowing, interrupting, arresting, or stopping of the progression of the diseases and conditions described herein, but does not necessarily indicate a total elimination of all disease and condition symptoms, and is intended to include prophylactic treatment and chronic use.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propanoic, succinic, tartaric, citric, methanesulfonic, benzenesulfonic, glucuronic, glutamic, benzoic, salicylic, toluenesulfonic, oxalic, fumaric, maleic, and the like. Further addition salts include ammonium salts such as tromethamine, meglumine, epolamine, etc., metal salts such as sodium, potassium, calcium, zinc or magnesium. Hydrochloride and oxalate salts are preferred.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418.

The compounds of the general formula (I) having geometrical and stereomers are also a part of the invention.

According to a further object, the present invention is also concerned with the
5 process of preparation of the compounds of formula (I).

The compounds and process of the present invention may be prepared in a number of ways well known to those skilled in the art. The compounds can be synthesized, for example, by application or adaptation of the methods described below, or variations thereon as appreciated by the skilled artisan. The appropriate modifications and substitutions will be
10 readily apparent and well known or readily obtainable from the scientific literature to those skilled in the art.

In particular, such methods can be found in R.C. Larock, *Comprehensive Organic Transformations*, VCH publishers, 1989.

It will be appreciated that the compounds of the present invention may contain one or
15 more asymmetrically substituted carbon atoms, and may be isolated in optically active or racemic forms. Thus, all chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. It is well known in the art how to prepare and isolate such optically active forms. For example, mixtures of stereomers may be separated by standard techniques
20 including, but not limited to, resolution of racemic forms, normal, reverse-phase, and chiral chromatography, preferential salt formation, recrystallization, and the like, or by chiral synthesis either from chiral starting materials or by deliberate synthesis of target chiral centers.

Compounds of the present invention may be prepared by a variety of synthetic routes.
25 The reagents and starting materials are commercially available, or readily synthesized by well-known techniques by one of ordinary skill in the arts. All substituents, unless otherwise indicated, are as previously defined.

In the reactions described hereinafter, it may be necessary to protect reactive functional groups, for example hydroxy, keto, amino, imino, thio or carboxy groups, where
30 these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in *Protective Groups in Organic Chemistry*, John Wiley and Sons, 1991; J. F. W. McOmie in *Protective Groups in Organic Chemistry*, Plenum Press, 1973.

35 Some reactions may be carried out in the presence of a base. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally

used in reactions of this type may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include: sodium hydroxide, potassium carbonate, triethylamine, alkali metal hydrides, such as sodium hydride and potassium hydride; alkyllithium compounds, such as methyllithium and butyllithium; and alkali metal alkoxides, such as sodium methoxide and sodium ethoxide.

Usually, reactions are carried out in a suitable solvent. A variety of solvents may be used, provided that it has no adverse effect on the reaction or on the reagents involved. Examples of suitable solvents include: hydrocarbons, which may be aromatic, aliphatic or cycloaliphatic hydrocarbons, such as hexane, cyclohexane, methylcyclohexane, toluene and xylene; amides, such as *N,N*-dimethylformamide; alcohols such as ethanol and methanol and ethers, such as diethyl ether, methyl *tert*-butyl ether, methyl cyclopentyl ether and tetrahydrofuran.

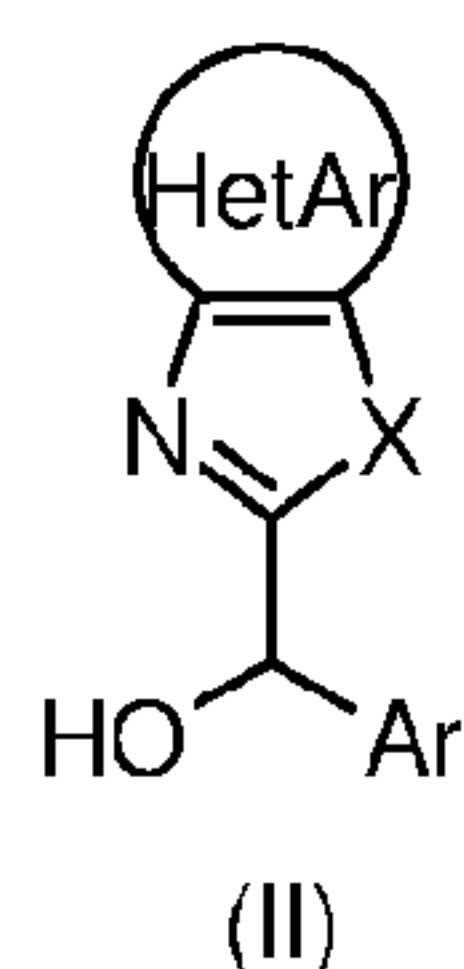
The reactions can take place over a wide range of temperatures. In general, we find it convenient to carry out the reaction at a temperature of from 0°C to 150°C (more preferably from about room temperature to 100°C). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 20 hours will usually suffice.

The compound thus prepared may be recovered from the reaction mixture by conventional means. For example, the compounds may be recovered by distilling off the solvent from the reaction mixture or, if necessary, after distilling off the solvent from the reaction mixture, pouring the residue into water followed by extraction with a water-immiscible organic solvent and distilling off the solvent from the extract. Additionally, the product can, if desired, be further purified by various well-known techniques, such as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography or preparative thin layer chromatography.

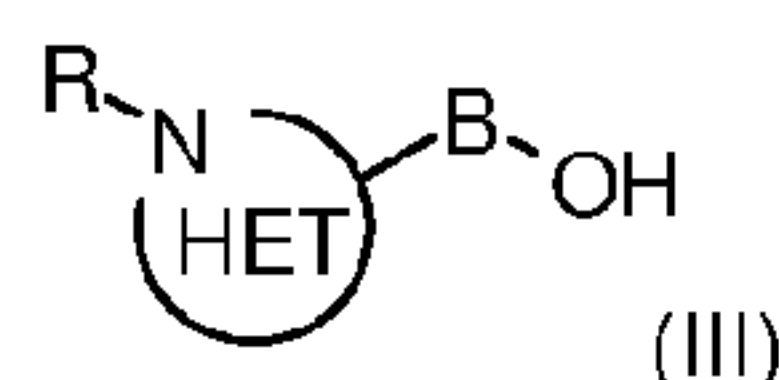
The process of preparation of a compound of formula (I) of the invention is another object of the present invention.

Compounds of formula (I) where A = O can be prepared by etherification of compound of formula (II):

40



in which X, HetAr and Ar are as defined in general formula (I)
with a compound of formula (III):



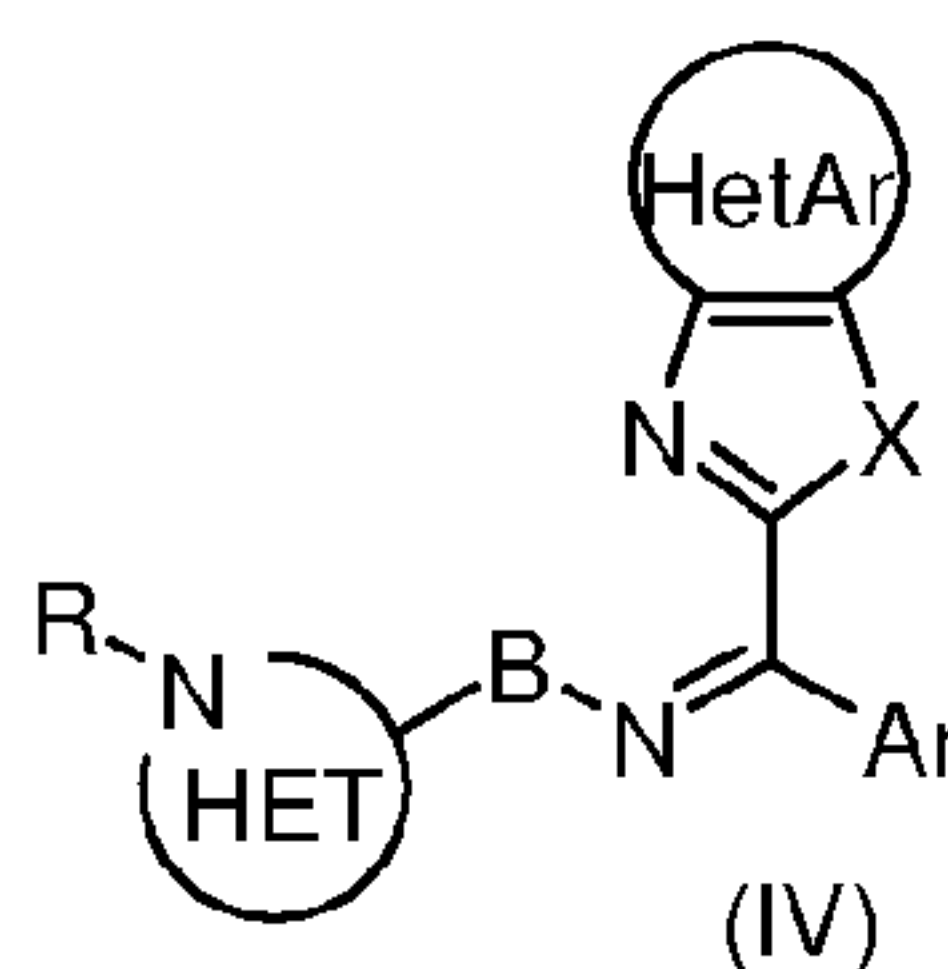
5 in which R, HET and B are as defined in general formula (I)

This etherification reaction can be performed in acidic medium (toluenesulfonic acid, methanesulfonic acid) in an inert solvent (toluene, dichlorobenzene, dichloroethane) at a temperature between room temperature and about 160°C.

10 Compounds of formula (II) can be prepared by condensing a benzothiazole or a benzimidazole derivative with an aldehyde ArCHO, by condensing an organometallic derivative ArMetal with an optionally substituted benzimidazole-2-carboxaldehyde or an optionally substituted benzothiazole-2-carboxaldehyde, or by condensing a hydroxy acid ArCHOHCOOH with an optionally substituted ortho-phenylenediamine or an optionally substituted 2-aminothiophenol or 2-aminophenol

15

Compounds of formula (I) wherein A = NH can be prepared by reduction of compound of formula (IV):



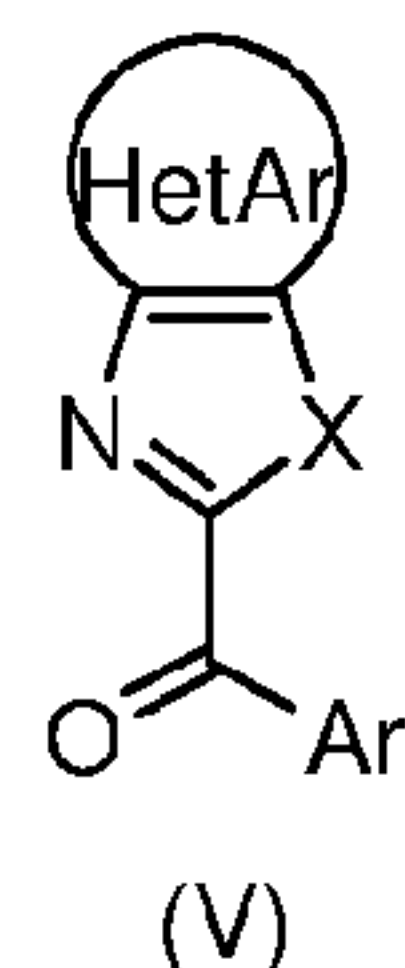
20 in which R, HET, B, X, HetAr and Ar are as defined in general formula (I)

This reduction can be performed by hydrogenation with dihydrogen or transfer hydrogenation (formic acid, formic acid / triethylamine, ammonium formate) in the presence of a catalyst (palladium on charcoal) in an inert solvent (methanol, ethanol, ethyl acetate) at a temperature comprised between room temperature and about 150°C.

25

41

Compounds of formula (IV) in which R, HET, B, X, HetAr and Ar are as defined in general formula (I) can be prepared by condensing compound of formula (V):



in which X, HetAr and Ar are as defined in general formula (I)

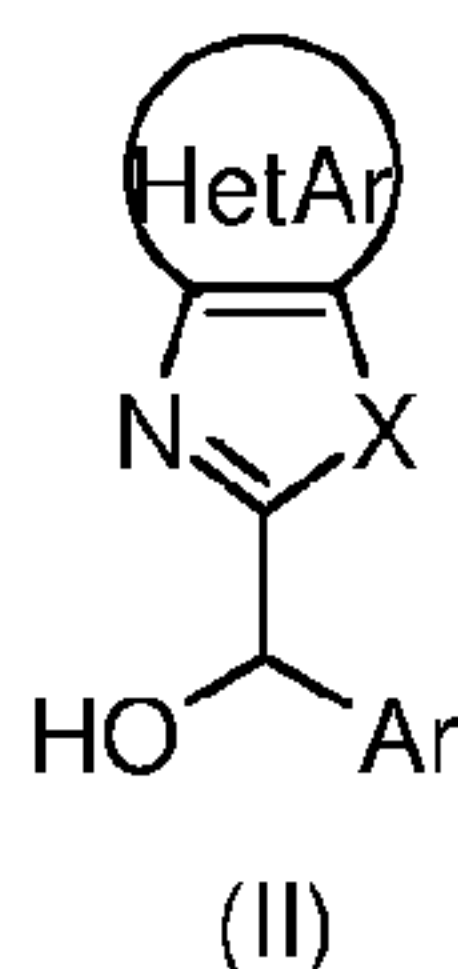


This condensation can be performed in the presence of an acid (titanium tetraisopropoxide) in an inert solvent (tetrahydrofurane) at a temperature comprised between room temperature and reflux of the medium.

10 Compounds of formula (V) in which X, HetAr and Ar are as defined in general formula (I) can be prepared by oxidizing compound of formula (II) in which X, HetAr and Ar are as defined in general formula (I).

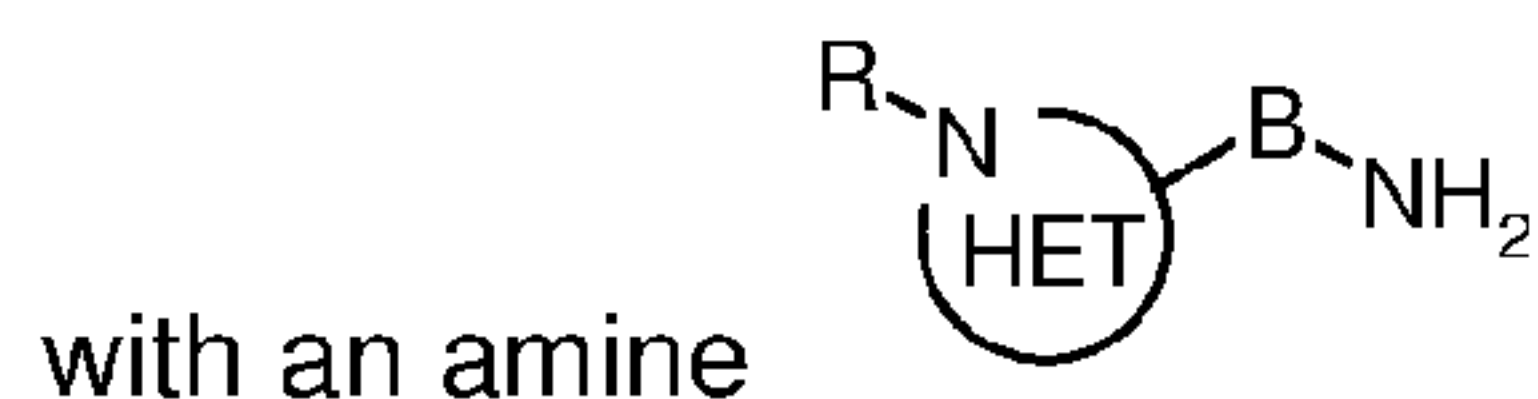
15 This oxidation can be performed with an oxidizing agent (potassium permanganate, barium permanganate, manganese dioxide) in an inert solvent (dioxane, acetonitrile) at a temperature comprised between room temperature and reflux of the medium.

Compounds of formula (I) where A = NH can be prepared by condensation of compound of formula (II):



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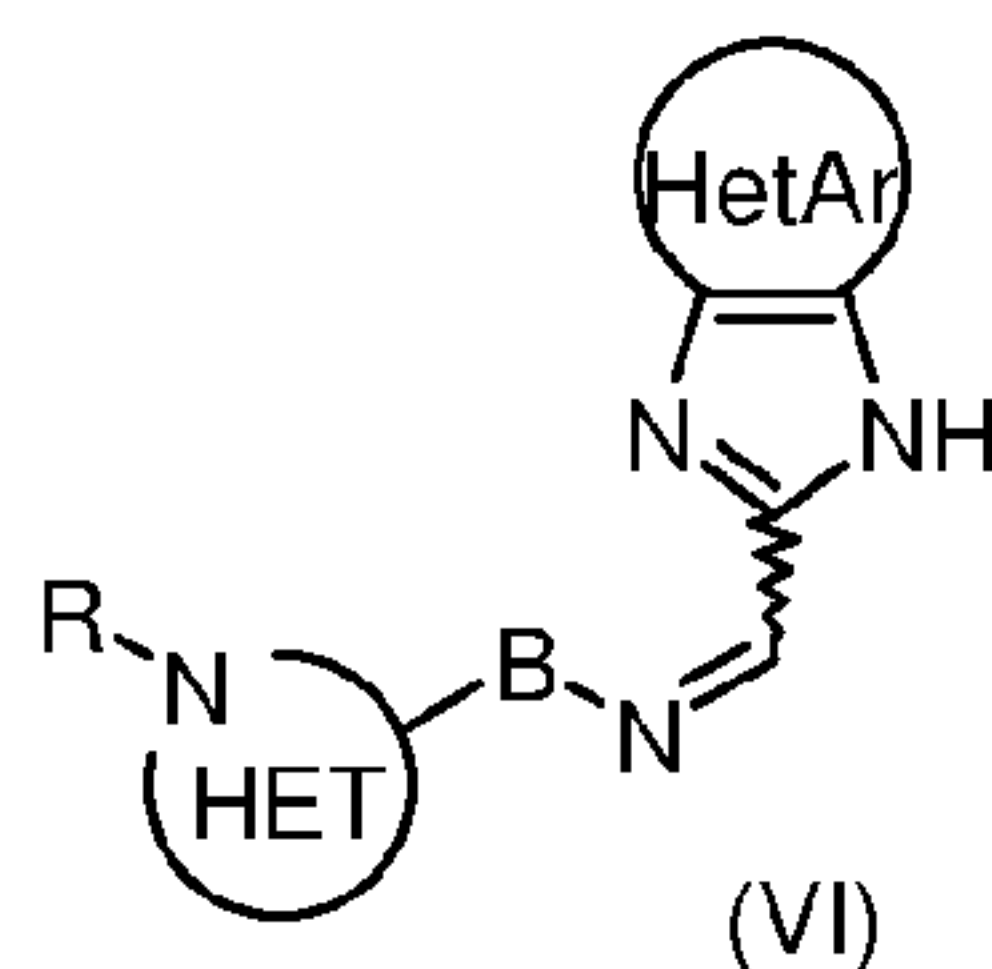
in which X, HetAr and Ar are as defined in general formula (I)



This condensation can be performed in the presence of a transition metal catalyst such as dichloro(pentamethylcyclopentadienyl)iridium(III) dimer, in the presence of a base

such as sodium hydrogenocarbonate in an inert solvent such as toluene at a temperature comprised between about 80 and 150 °C.

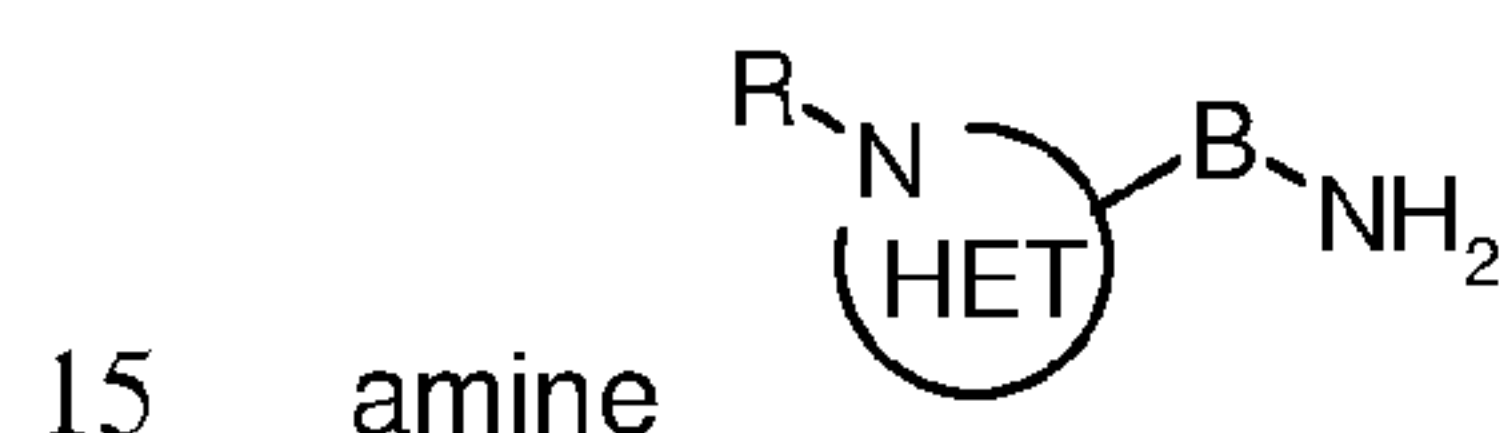
- Alternatively, compounds of formula (I) in which A and X are NH can be prepared
5 by condensing an organometallic reagent ArM onto a compound of formula (VI):



in which R, HET, B, HetAr and Ar are as defined in general formula (I)

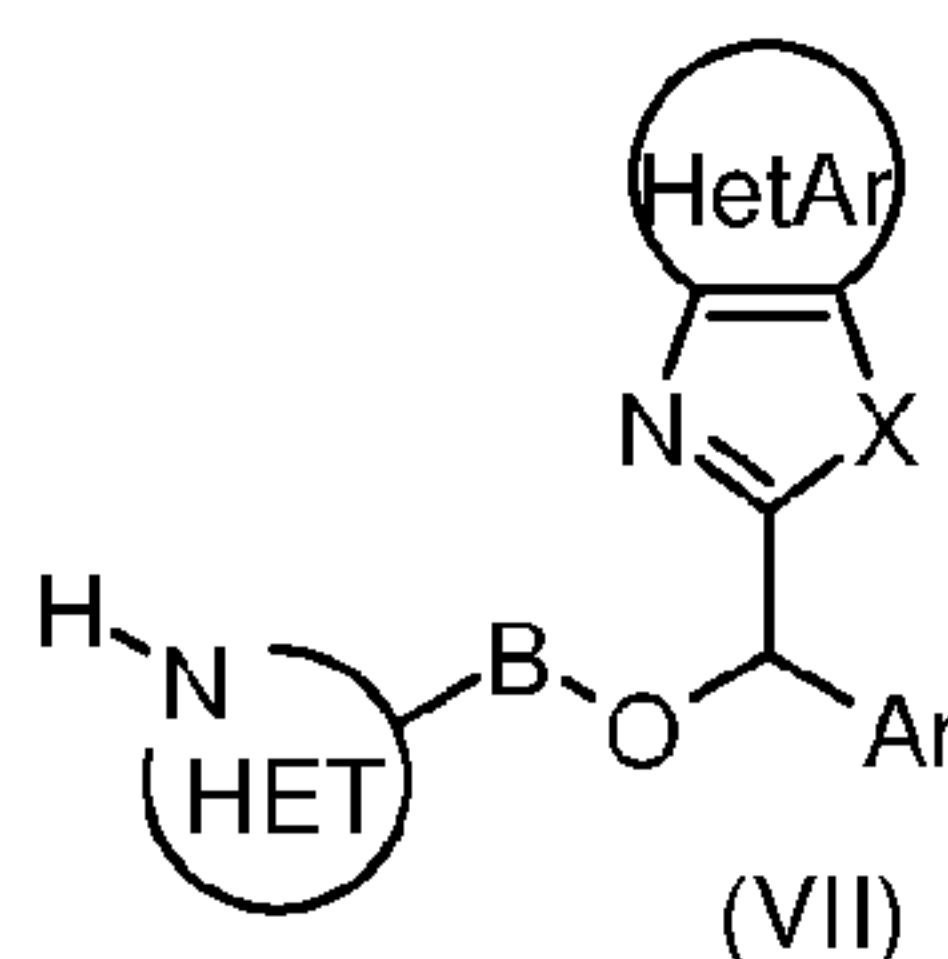
- This addition can be performed by adding a Grignard reagent onto an imine in an
inert solvent (tetrahydrofurane) at a temperature comprised between room temperature
10 and reflux of the medium.

Compounds of formula (VI) in which R, HET, B, HetAr and Ar are as defined in
general formula (I) can be prepared by condensing an optionally substituted
benzimidazole-2-carboxaldehyde or heteroaryl fused imidazole-2-carboxaldéhyde with an



This condensation can be performed in the presence of molecular sieves or other
dehydrating agent in an inert solvent (ethanol) at a temperature comprised between 40 °C
and the refluxing temperature. A Dean Stark apparatus can also be used.

- Alternatively, compounds of formula (I) in which A=O can be prepared by alkylation
20 of compound of formula (VII):

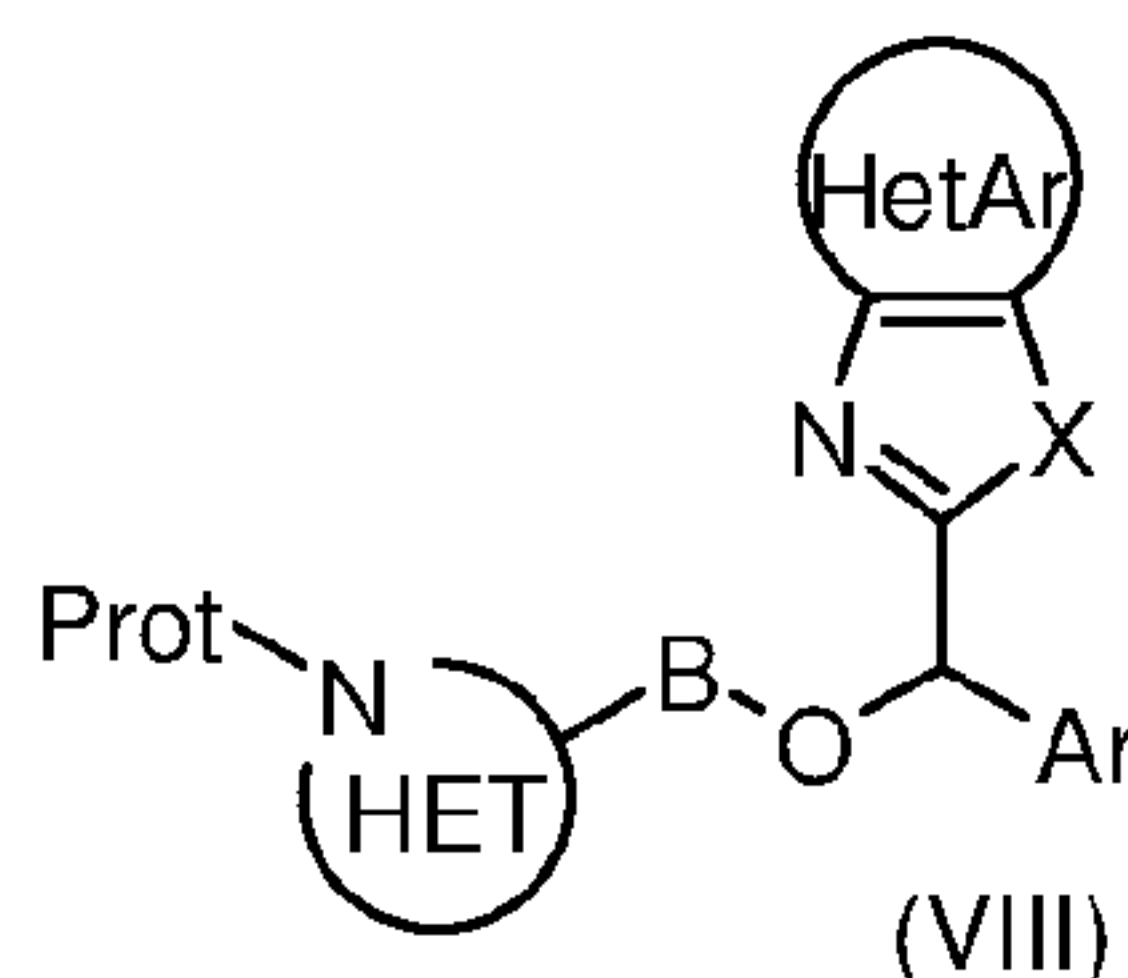


in which HET, B, X, HetAr and Ar are as defined in general formula (I)

- This alkylation can be performed by reductive method using a carbonylated
25 compound and a reducing agent such as a borohydride, a cyanoborohydride, a
triacetoxyborohydride, hypophosphonous acid, formic acid, formic acid / triethylamine or

hydrogen, a catalyst such as palladium can be added for this transformation when hydrogen or hydrogen donors are used.

Compounds of formula (VII) can be prepared by deprotection of compound of
5 formula (VIII):

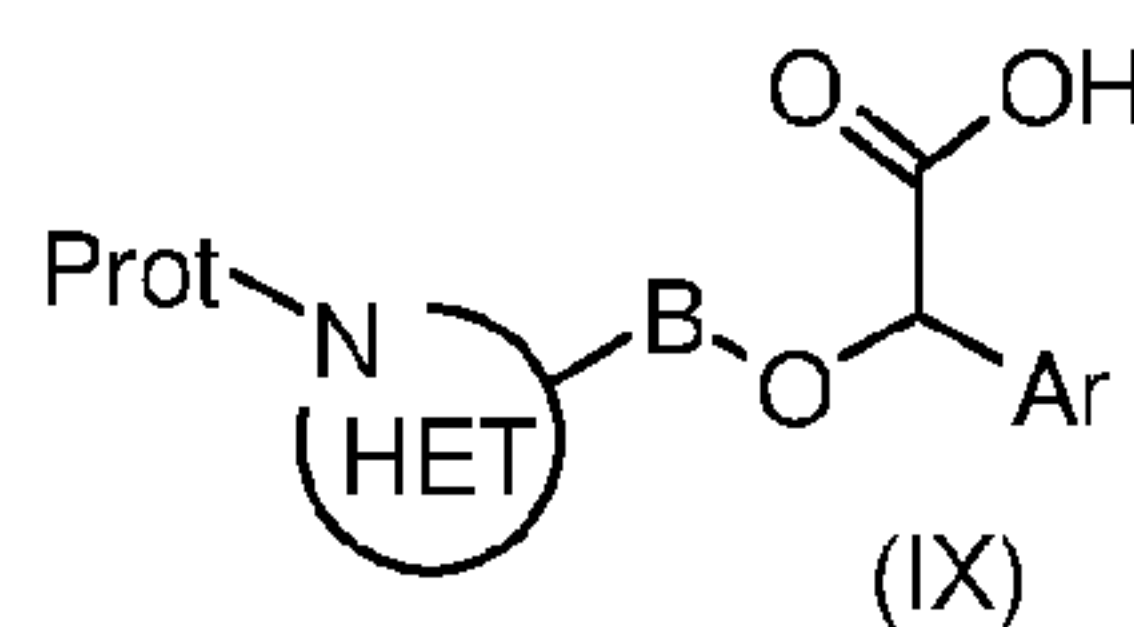


in which HET, B, X, HetAr and Ar are as defined in general formula (I) and Prot is a protecting group of the nitrogen atom.

When Prot is a *tert*-butoxycarbonyl group, the transformation is usually performed
10 in acidic medium such as trifluoroacetic acid diluted with dichloromethane or in a solvent (ethyl acetate, ethanol, isopropanol) containing HCl. Preferably, this deprotection is performed at a temperature between 0°C and the refluxing temperature of the medium.

Compounds of formula (VIII) in which HET, B, X, HetAr and Ar are as defined in
15 general formula (I) and Prot is a protecting group of the nitrogen atom can be prepared using the general methods described above.

Alternatively, compounds of formula (VIII) in which A= O and HET, B, X, HetAr and
Ar are as defined in general formula (I) and Prot is a protecting group of the nitrogen atom
20 can be prepared by condensing an acid of formula (IX):

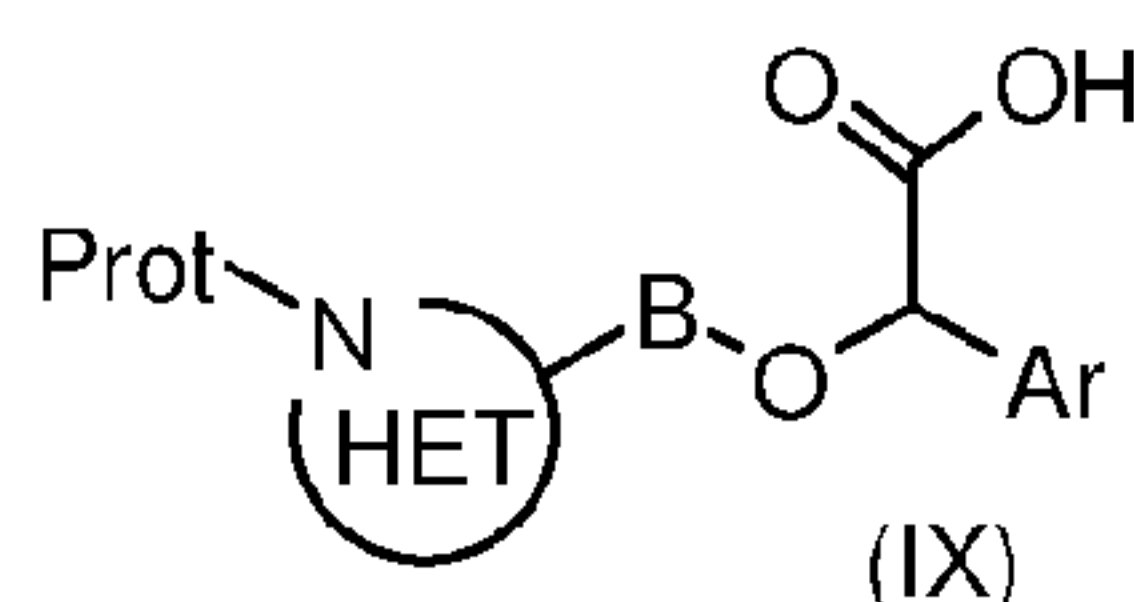


in which HET, B and Ar are as defined in general formula (I) and Prot is a protecting group of the nitrogen atom,

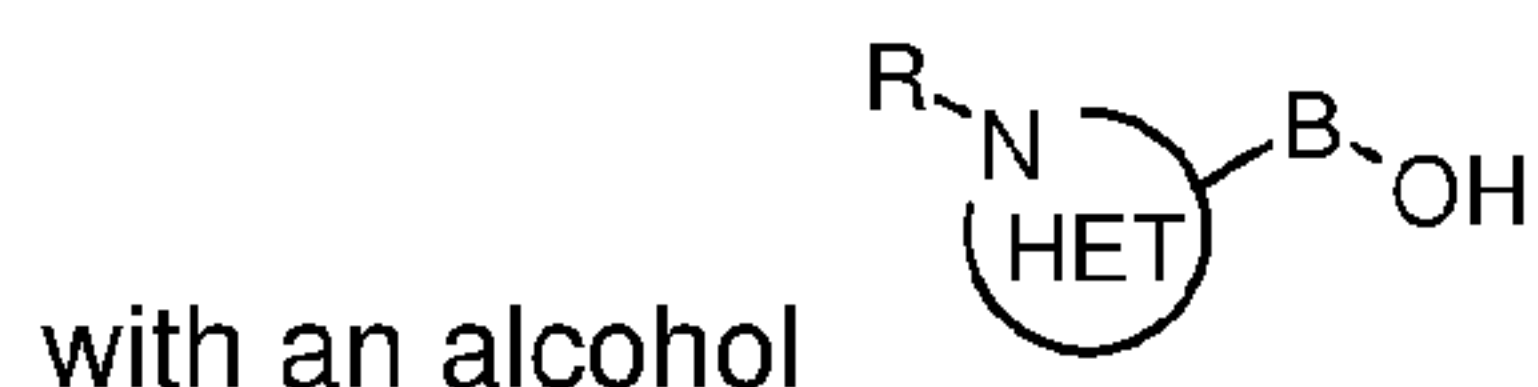
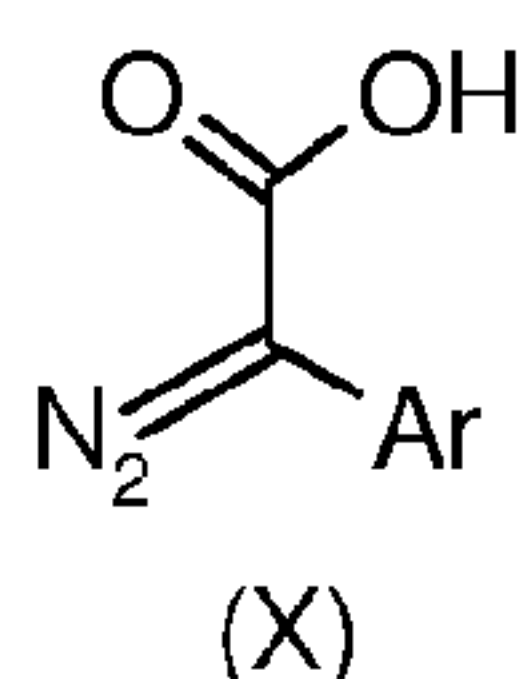
with an optionally substituted ortho-phenylenediamine or an optionally substituted
25 2-aminothiophenol.

This condensation can be performed by reacting the two compounds in acidic medium, or by first forming the amide bond with usual bond forming reagents, then dehydrating in acidic medium (acetic acid, hydrochloric acid) at a temperature comprised between room temperature and reflux.

Acids of formula (IX) in which HET, B and Ar are as defined in general formula (I) and Prot is a protecting group of the nitrogen atom can be prepared by hydrolysis of their esters. This hydrolysis can be performed in basic medium or in acidic medium at a temperature comprised between 0 °C and reflux of the medium.



Esters of the acid of formula (IX) in which HET, B, X and Ar are as defined in general formula (I) and Prot is a protecting group of the nitrogen atom can be prepared by condensing an ester of the acid (X)



This condensation can be performed in the presence of a metal catalyst such as rhodium acetate dimer in an inert solvent such as dichloromethane or dichloroethane, at a temperature comprised between 0 °C and reflux of the medium.

Esters of the acid of formula (X) can be prepared from esters of an acid ArCH_2COOH with a diazo transfer reagent such as tosylazide in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene in an inert solvent such as acetonitrile at a temperature comprised between -20 °C and 40 °C.

Furthermore, compounds of formula (I) can be prepared from compounds of formula (I) by group interconversion or group transformation. Such reaction include, but are not limited to, reaction on aromatic or heteroaromatic groups such as halogen exchange reaction, Sonogashira reaction, Heck reaction, Suzuki reaction, sulfide condensation, triflate displacement with grignard reagents, copper catalysed ether formation, metal catalysed amine aromatic substitution, aromatic carbonylation reaction; reaction on reactive groups such as acylation, alcoxycarbonylation of nitrogen containing groups such as amines, amidines, guanidines; substitution of hydroxy with nucleophile

(Mitsunobu reaction or activation and nucleophilic substitution); hydrogenation of unsaturation (alkenyl to alkyl, alkynyl to alkenyl, alkynyl to alkyl); Staudinger reduction of azido group.

- 5 The process of the invention may comprise the additional step of isolating the desired compound of formula (I).

 The starting products and/or reagents may be commercially available, or may be readily prepared by the skilled person by applying or adapting the procedures disclosed in
10 the experimental part below.

 According to a still further object, the present invention is also concerned with pharmaceutical compositions comprising a compound of formula (I) as defined above with a pharmaceutically acceptable excipient.

- 15 The compounds of the invention are antagonists and/or inverse agonists of H₄ R. The pharmaceutical compositions and compounds of the invention may thus be useful for use in the treatment and/or prevention of a disease associated with H₄ dysfunction, such as inflammatory disorders.

 Said disease includes adult respiratory distress syndrome, acute respiratory
20 distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis, chronic sinusitis, allergy, allergy induced airway responses, allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, conjunctivitis, nasal congestion, allergic congestion; disorders of the genito-urinary tract such as female and male sexual dysfunction, overactive bladder
25 conditions, urinary incontinence, bladder overactivity, benign prostate hyperplasia and lower urinary tract symptoms; dermatological diseases such as dermatitis and psoriasis and treatment of itchy skin; diseases of the cardiovascular system including thromboembolic diseases, atherosclerosis, myocardial infarction, angina pectoris, myocardial ischaemia and arrhythmia, peripheral arterial occlusive diseases, pulmonary
30 embolisms or deep venous thromboses, hypotension, pulmonary hypertension, malignant hypertension, cardiac insufficiency, heart or kidney failure, stroke and renal dysfunction; diseases of the gastrointestinal tract including inflammatory bowel disease, Crohn's disease, ulcerative colitis; autoimmune diseases including rheumatoid arthritis, multiple sclerosis; cancer; pain; lymphatic diseases.

According to a further object, the present invention also concerns a combination of a compound of the invention with one or more therapeutic agent(s) selected from:

- Histamine H₁, H₂ or H₃ receptor antagonists,
- Leukotriene antagonists,
- 5 • 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists
- CX₁- and α_2 -adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use
- Xanthines, such as theophylline and aminophylline
- 10 • Non-steroidal antiinflammatories, such as sodium cromoglycate and nedocromil sodium
- Ketotifen
- COX-1 inhibitors (NSAIDs) and COX-2 selective inhibitors
- Immunosuppressants
- 15 • mucolytics or anti-tussive agents

More particularly, the present invention also concerns combinations comprising a compound of formula (I) of the invention with a H1R antagonist, such as cetirizine, desloratadine, bepotastine or doxepin.

20 According to a still further object, the present invention is also concerned with a compound of formula (I) for the above conditions to be administered to a patient in the need thereof.

25 According to a still further object, the present invention also concerns the methods of treatment comprising administering an effective amount of a compound of the invention for treating and/or preventing the above conditions or disorders.

30 The identification of those subjects who are in need of treatment of herein-described diseases and conditions is well within the ability and knowledge of one skilled in the art. A clinician skilled in the art can readily identify, by the use of clinical tests, physical examination and medical/family history, those subjects who are in need of such treatment.

35 A therapeutically effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective amount, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of subject; its size, age, and

general health; the specific disease involved; the degree of involvement or the severity of the disease; the response of the individual subject; the particular compound administered; the mode of administration; the bioavailability characteristic of the preparation administered; the dose regimen selected; the use of concomitant medication; and other
5 relevant circumstances.

The amount of a compound of formula (I), which is required to achieve the desired biological effect, will vary depending upon a number of factors, including the dosage of the drug to be administered, the chemical characteristics (e.g. hydrophobicity) of the compounds employed, the potency of the compounds, the type of disease, the diseased
10 state of the patient, and the route of administration.

In general terms, the compounds of this invention may be provided in an aqueous physiological buffer solution containing 0.1 to 10% w/v compound for parenteral administration. Typical dose ranges are from 1 µg/kg to 0.1 g/kg of body weight per day; a preferred dose range is from 0.01 mg/kg to 10 mg/kg of body weight per day. A preferred
15 daily dose for adult humans includes 1, 5, 50, 100 and 200 mg, and an equivalent dose in a human child. The preferred dosage of drug to be administered is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, and formulation of the compound excipient, and its route of administration.

The compounds of the present invention are capable of being administered in unit dose forms, wherein the term "unit dose" means a single dose which is capable of being administered to a patient, and which can be readily handled and packaged, remaining as a physically and chemically stable unit dose comprising either the active compound itself, or as a pharmaceutically acceptable composition, as described hereinafter. As such,
25 typical daily dose ranges are from 0.01 to 10 mg/kg of body weight. By way of general guidance, unit doses for humans range from 0.1 mg to 1000 mg per day. Preferably, the unit dose range is from 1 to 500 mg administered one to four times a day, and even more preferably from 1 mg to 300 mg, once a day. Compounds provided herein can be formulated into pharmaceutical compositions by admixture with one or more
30 pharmaceutically acceptable excipients. Such compositions may be prepared for use in oral administration, particularly in the form of tablets or capsules; or parenteral administration, particularly in the form of liquid solutions, suspensions or emulsions; or intranasally, particularly in the form of powders, nasal drops, or aerosols; or dermally, for example, topically or via trans-dermal patches or ocular administration, or intravaginal or
35 intra-uterine administration, particularly in the form of pessaries or by rectal administration.

The compositions may conveniently be administered in unit dosage form and may be prepared by any of the methods well known in the pharmaceutical art, for example, as described in Remington: *The Science and Practice of Pharmacy*, 20th ed.; Gennaro, A. R., Ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2000. Pharmaceutically compatible
5 binding agents and/or adjuvant materials can be included as part of the composition. Oral compositions will generally include an inert diluent carrier or an edible carrier.

The tablets, pills, powders, capsules, troches and the like can contain one or more of any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, or gum tragacanth; a diluent such as starch or lactose; a
10 disintegrant such as starch and cellulose derivatives; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, or methyl salicylate. Capsules can be in the form of a hard capsule or soft capsule, which are generally made from gelatin blends optionally blended with plasticizers, as well as a starch capsule. In addition,
15 dosage unit forms can contain various other materials that modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents. Other oral dosage forms syrup or elixir may contain sweetening agents, preservatives, dyes, colorings, and flavorings. In addition, the active compounds may be incorporated into fast dissolve, modified-release or sustained-release preparations and formulations, and wherein such
20 sustained-release formulations are preferably bi-modal.

Preferred formulations include pharmaceutical compositions in which a compound of the present invention is formulated for oral or parenteral administration, or more preferably those in which a compound of the present invention is formulated as a tablet.
25 Preferred tablets contain lactose, cornstarch, magnesium silicate, croscarmellose sodium, povidone, magnesium stearate, or talc in any combination. It is also an aspect of the present disclosure that a compound of the present invention may be incorporated into a food product or a liquid.

Liquid preparations for administration include sterile aqueous or non-aqueous
30 solutions, suspensions, and emulsions. The liquid compositions may also include binders, buffers, preservatives, chelating agents, sweetening, flavoring and coloring agents, and the like. Non-aqueous solvents include alcohols, propylene glycol, polyethylene glycol, acrylate copolymers, vegetable oils such as olive oil, and organic esters such as ethyl oleate. Aqueous carriers include mixtures of alcohols and water, hydrogels, buffered
35 media, and saline. In particular, biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be

useful excipients to control the release of the active compounds. Intravenous vehicles can include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Other potentially useful parenteral delivery systems for these active compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes.

Alternative modes of administration include formulations for inhalation, which include such means as dry powder, aerosol, or drops. They may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for buccal administration include, for example, lozenges or pastilles and may also include a flavored base, such as sucrose or acacia, and other excipients such as glycocholate. Formulations suitable for rectal administration are preferably presented as unit-dose suppositories, with a solid based carrier, such as cocoa butter, and may include a salicylate. Formulations for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include petroleum jelly, lanolin, polyethylene glycols, alcohols, or their combinations. Formulations suitable for transdermal administration can be presented as discrete patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive.

Alternative administrations include also solutions, ointments or other formulations acceptable for ocular administration.

Other features of the invention will become apparent in the course of the following description of exemplary embodiments that are given for illustration of the invention and not intended to be limiting thereof.

Examples

Melting points are determined on Büchi capillary melting point apparatus.

Proton NMR spectra are recorded on a Bruker™ 250 MHz NMR instrument. Deuteriochloroform is used as solvent unless otherwise stated. The chemical shifts δ are expressed in ppm. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, ms = massif. The coupling constants are expressed in Hz. The spectra recorded are consistent with the proposed structures.

TLC are performed on 0.25 mm silica gel F254 plates.

Example 1 2-[(1-methylpiperidin-4-yloxy)phenylmethyl]benzothiazole

1A

A mixture of benzothiazol-2-ylphenylmethanol (0.36g), 4-hydroxy-1-methylpiperidine (0.17g) and para-toluenesulfonic acid (0.57g) in toluene (22mL) is heated overnight in a Dean-Stark apparatus. The mixture is cooled back to room temperature and poored into water, alcalinised with 1N sodium hydroxyde and extracted twice with ethyl acetate. Pooled organic extracts are washed with brine, dried over magnesium sulfate and concentrated. The residue is purified by column chromatography over silica gel (gradient dichloromethane/methanol from 98/2 to 90/10) to give 2-[(1-methylpiperidin-4-yloxy)phenylmethyl]benzothiazole melting at 115 °C.

1B

A solution of benzothiazole (1.35g) in tetrahydrofurane (10mL) in a dried round bottom baloon is cooled at -70 °C. A solution of butyl lithium (4.1mL) is added and the mixture stirred for 15 minutes. Benzaldehyde (1.03mL) diluted with tetrahydrofurane (10mL) is then added. The mixture is stirred at -70 °C for 1h, allowed to warm to -20 °C and quenched with saturated aqueous ammonium chloride solution. The mixture is extracted with ethyl acetate. Organic extracts are pooled, dried over magnesium sulfate and concentrated under reduced pressure. Trituration of the residue with diisopropyl oxyde affords benzothiazol-2-ylphenylmethanol.

TLC (heptane/ethyl acetate 1/1) R_f = 0.57

Further examples can be prepared according to the described general methods:

Example	Product	General methods	Melting point
2	2-[(1-methylpyrrolidin-3-yloxy)phenylmethyl]-benzothiazole, oxalate	1A, 1B	120 °C
3	2-[(4-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	192 °C
4	2-[(4-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	147-148 °C
5	2-[(3-fluorophenyl)(1-methylpiperidin-4-yloxymethyl]benzothiazole, oxalate	1A, 1B	167-170 °C
6	2-[(2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	178-179 °C

Example	Product	General methods	Melting point
7	2-[(1-methylpiperidin-4-yloxy)-p-tolylmethyl]benzothiazole, oxalate	1A, 1B	177 °C
8	2-[(1-methylpiperidin-4-yloxy)(m-tolyl)methyl]benzothiazole, oxalate	1A, 1B	177 °C
10	2-[(2,3-dihydrobenzo[1,4]dioxin-6-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, hydrochloride	1A, 1B	71 °C
11	2-[(3-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, hydrochloride	1A, 1B	182 °C
12	2-[(2,4-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, dioxalate	1A, 1B	182 °C
14	2-[(4-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, dihydrochloride	1A, 1B	72 °C
15	2-[(3,5-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	165 °C

Following compounds are prepared using general methods described in Example 1:

Example	Product
9	(benzothiazol-2-yl-phenylmethyl)(1-methylpiperidin-4-yl)amine
	¹ H NMR: 8.00 (d, 1H), 7.90 (d, 1H), 7.55-7.35 (m, 2H), 7.32 (d, 1H), 7.10 (d, 1H), 6.98 (d, 1H), 6.17 (s, 1H), 3.80-3.65 (m, 1H), 2.80-2.65 (m, 2H), 2.29 (s, 3H),), 2.28-2.15 (m, 2H), 2.10-1.80 (m, 4H)
13	2-[(1-methylpiperidin-4-yloxy)thiophen-2-ylmethyl]benzothiazole
	¹ H NMR: 7.95 (d, 1H), 7.84 (d, 1H), 7.52 (m, 2H), 7.50-7.25 (m, 5H), 5.44 (s, 1H), 3.88-3.75 (m, 2H), 3.65-3.50 (m, 1H), 2.24 (s, 3H),), 2.15-1.85 (m, 4H), 1.65-1.35 (m, 2H)
23	2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethoxyphenyl)methyl]benzothiazole, oxalate
	¹ H NMR (DMSO-d ⁶): 7.99 (d, 1H), 7.87 (d, 1H), 7.55-7.35 (m, 5H), 7.27-7.15 (m, 1H), 6.11 (s, 1H), 3.95-3.80 (m, 1H), 3.50-3.00 (m, 6H), 2.79 (s, 3H),), 2.20-1.70 (m, 4H),

Example 16

5

16 A

A mixture of (benzothiazol-2-yl)(thien-3-yl)methanol (0.247g), 4-hydroxy-1-methylpiperidine (0.115g) and para-toluenesulfonic acid (0.27g) in dichloroethane (20mL)

is heated for 4H in a Dean-Stark apparatus. The mixture is concentrated under reduced pressure and the residue taken up in ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate and concentrated. The residue is purified by column chromatography over silica gel (gradient dichloromethane/methanol from 100/0 to 95/5).

- 5 Salification with oxalic acid in acetone gives -[(1-methylpiperidin-4-yloxy)thiophen-3-ylmethyl]benzothiazole oxalate melting at 174 °C.

16B (benzothiazol-2-yl)(thien-3-yl)methanol is prepared according to general method 1B.

10

Example 21

21A

- A solution of [(benzothiazol-2-yl)(m-tolyl)methylene](1-methylpiperidin-4-yl)amine (0.45g) in methanol (30mL) containing 10% palladium on charcoal (0.1g) is stirred under
15 dihydrogene (1atm) at room temperature for 3h. The suspension is filtered over clarcel and concentrated under reduced pressure. The residue is dissolved in acetone (2mL) and mixed with a solution of oxalic acid (76mg) in acetone (2mL). A precipitate forms which is filtered, rinsed with acetonitrile and diethyl ether and dried under vacuum to afford
20 [(benzothiazol-2-yl)(m-tolyl)methyl](1-methylpiperidin-4-yl)amine dioxalate melting at 127 °C.

21B

- To a solution of (benzothiazol-2-yl)(m-tolyl)methanone (1.06g) and 4-amino-1-methylpiperidine (0.456g) in tetrahydrofurane (4mL) is added titanium tetraisopropoxyde
25 (1.42g). The mixture is stirred at room temperature for 1h, then polymethyl hydrosiloxane (1.2mL) is added. The mixture is stirred for one day at room temperature, diluted with ethyl acetate (50mL), hydolysed with 3N sodium hydroxyde (30mL). The organic phase is separated by decantation, washed with water, dried over magnesium sulfate and concentrated in vacuo. The residue is cristallised by trituration in diisopropyl oxyde. A
30 second crop can be obtained form the mother liquor by chromatography over silica gel (gradient dichloromethane / methanol from 98 / 2 to 95 / 5) to give [(benzothiazol-2-yl)(m-tolyl)methylene](1-methylpiperidin-4-yl)amine meting at 125 °C.

21C

- To a solution of (benzothiazol-2-yl)(m-tolyl)methanol (2.41g) in dioxane (30mL) is
35 added manganese dioxyde (1.2 molar equivalent). The mixture is stirred overnight at room temperature, then filtered over a clarcel pad. The filtrate is concentrated under reduced

pressure. The residue is triturated in heptane and diisopropyl oxyde to give (benzothiazol-2-yl)(m-tolyl)methanone

21D (benzothiazol-2-yl)(m-tolyl)methanol can be obtained as described in Example 1B.

5

Further examples can be prepared according to the described general methods:

Example	Product	General methods	Melting point
17	2-[(1-methylpiperidin-4-yloxy)naphthalen-1-ylmethyl]benzothiazole	1A, 1B	106,5 °C
18	2-[(1-methylpiperidin-4-yloxy)naphthalen-2-ylmethyl]benzothiazole, dihydrochloride	1A, 1B	198 °C
19	2-[(1-methylpiperidin-4-yloxy)(5-methylthiophen-2-yl)methyl]benzothiazole, oxalate	16A, 1B	174 °C
20	2-[benzo[1,3]dioxol-5-yl(1-methylpiperidin-4-yloxy)methyl]benzothiazole, dihydrochloride	1A, 1B	110 °C
24	2-[(1-methylpiperidin-4-yloxy)(4-trifluoromethoxyphenyl)methyl]benzothiazole, oxalate	1A, 1B	155 °C
25	[benzothiazol-2-yl(3-methoxyphenyl)methyl](1-methylpiperidin-4-yl)amine, dioxalate	21A, 21B, 21C, 1B	160 °C
27	2-[(3-bromo-phenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole	1A, 1B	99 °C
28	2-[(1-methylpiperidin-4-yloxy)(3-phenoxy-phenyl)methyl]benzothiazole, oxalate	1A, 1B	92 °C
29	5-methyl-2-[(1-methylpiperidin-4-yloxy)phenylmethyl]benzothiazole, oxalate	1A, 1B	175 °C
30	2-[(1-methylpiperidin-4-yloxy)phenylmethyl]-1H-benzimidazole	1A, 1B	110 °C
31	2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethylphenyl)methyl]benzothiazole, hydrochloride	1A, 1B	61 °C
34	2-[(4-fluoro-3-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	120 °C
35	[benzothiazol-2-yl(4-fluoro-3-methyl-phenyl)methyl](1-methylpiperidin-4-yl)amine, dioxalate	1A, 1B	160 °C

Example	Product	General methods	Melting point
36	(benzothiazol-2-yl-p-tolylmethyl)(1-methylpiperidin-4-yl)amine, oxalate	1A, 1B	110 °C
38	2-[(3-fluoro-5-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	170 °C

Example 26

To a solution of 2-[(3-allyloxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole example 22 (250mg) in ethanol (10mL) is added 10% palladium on charcoal (25mg). The mixture is stirred overnight under dihydrogene (1atm) at room temperature, then filtrated over a clarcel pad. The filtrate is concentrated under reduced pressure to give the crude base which is converted to 2-[(1-methylpiperidin-4-yloxy)(3-propoxy-phenyl)methyl]benzothiazole, dihydrochloride melting at 59 °C.

Following compounds are prepared using general methods described in example 1:

Example	Product
33	5-fluoro-2-[(1-methylpiperidin-4-yloxy)phenylmethyl]benzothiazole
¹ H NMR: 7.80 (dd, 1H), 7.65 (dd, 1H), 7.58-7.68 (m, 2H), 7.45-7.28 (m, 3H), 7.14 (dt, 1H), 5.89 (s, 1H), 3.80-3.60 (m, 1H), 2.90-2.72 (m, 2H), 2.38 (s, 3H), 2.15-1.70 (m, 6H)	

Example 37

37A

Reduction of [(benzofuran-2-yl)(benzothiazol-2-yl)methylene](1-methylpiperidin-4-yl)amine as described in example 21A affords [(benzofuran-2-yl)(benzothiazol-2-yl)methyl](1-methylpiperidin-4-yl)amine oxalate melting at 125 °C.

37B

To a solution of (benzofuran-2-yl)(benzothiazol-2-yl)methanone (1.4g) and 4-amino-1-methylpiperidine (0.57g) in tetrahydrofurane (8mL) is added dropwise titanium tetraisopropoxyde (1.78g). The suspension is stirred for 24h at room temperature, diluted with ethyl acetate and 1N sodium hydroxyde. The precipitate is filtered over a clarcel pad and rinsed with ethyl acetate. The pooled filtrates are washed with saturated sodium chloride solution, dried and concentrated under reduced pressure. The residue is purified

over silica gel (gradient dichloromethane / methanol from 100 / 0 to 90 / 10) to afford [(benzofuran-2-yl)(benzothiazol-2-yl)methylene](1-methylpiperidin-4-yl)amine.

37C (benzofuran-2-yl)(benzothiazol-2-yl)methanone can be prepared as described
5 in example 21C.

37D (benzofuran-2-yl)(benzothiazol-2-yl)methanone can be prepared as described
in example 1B.

10 Further examples can be prepared according to the described general methods:

Example	Product	General methods	Melting point
39	[(1 <i>H</i> -benzimidazol-2-yl)phenylmethyl](1-methylpiperidin-4-yl)amine	21A, 37B, 21C, 1B	133 °C
40	2-[(3-fluoro-5-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	145 °C
41	2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	165-170 °C

Example 42

15 [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
42A

Hydrogenation of [benzothiazol-2-yl(3-propoxyphenyl)methylene](1-methylpiperidin-4-yl)amine as described in example 21A gives [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine melting at 90 °C.

20 42B

Condensation of benzothiazol-2-yl(3-propoxyphenyl)methanone with 4-amino-1-methylpiperidine as described in example 37B gives [benzothiazol-2-yl(3-propoxyphenyl)methylene](1-methylpiperidin-4-yl)amine.

25 42C

A mixture benzothiazol-2-yl(3-propoxyphenyl)methanol (1g) and barium permanganate (0.95g) in acetonitrile 15mL) is refluxed for 30 minutes. The mixture is filtered over a clarcel pad, concentrated under reduced pressure and purified by column

chromatography over silica gel (eluant heptane / ethyl acetate : 4 / 1) to give benzothiazol-2-yl(3-propoxyphenyl)methanone as a white cristalline solid.

42D

- 5 Benzothiazol-2-yl(3-propoxyphenyl)methanol can be prepared as described in example 1B.

Further examples can be prepared according to the described general methods:

Example	Product	General methods	Melting point
43	[benzothiazol-2-yl(3-fluoro-5-methoxyphenyl)methyl](1-methylpiperidin-4-yl)amine, oxalate	21A, 37B, 21C, 1B	157 °C
44	[benzothiazol-2-yl(3-fluoro-5-methylphenyl)methyl](1-methylpiperidin-4-yl)amine	21A, 37B, 21C, 1B	102 °C
45	2-[(3-benzyloxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	52 °C
46	2-[benzofuran-5-yl(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	153 °C
47	2-[(3-ethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	84 °C
48	[benzothiazol-2-yl(3-iodophenyl)methyl](1-methylpiperidin-4-yl)amine, oxalate	21A, 37B, 21C, 1B	188-195 °C
49	2-[(1-methylpiperidin-4-yloxy)(3-propoxyphenyl)methyl]-1 <i>H</i> -benzimidazole	1A, 1B	135 °C
50	[(1 <i>H</i> -benzimidazol-2-yl)(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine	21A, 37B, 21C, 1B	143 °C
51	2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	1A, 1B	173,5 °C
52	(benzothiazol-2-ylpyridin-3-ylmethyl)(1-methylpiperidin-4-yl)amine	21A, 37B, 42C, 1B	109 °C

A mixture of 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (200mg), phenylboronic acid (70mg), palladium acetate (4.8mg) and 1,1-bis(diphenylphosphino)ferrocene is placed in a round-bottom flask and purged with argon.

A 1M aqueous degased solution of potassium carbonate (1.51mL) and degased tetrahydrofuran (2mL) are introduced. The mixture is heated at 95°C for 30min, cooled back to room temperature and filtered over a celite™ pad. The cake is rinsed with ethyl acetate and water. The pooled phases are decanted. The organic phase is dried over magnesium sulfate and concentrated. The residue is purified by column chromatography (gradient dichloromethane / methanol from 98 / 2 to 90 / 10) to give the crude base which is then converted to the oxalate in acetone to give 2-[biphenyl-3-yl(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate as a beige amorphous solid.

¹H NMR (DMSO-d⁶): 8.05 (d, 1H), 7.91 (d, 1H), 7.77 (s, 1H), 7.68-7.58 (m, 3H), 7.55-7.30 (m, 7H), 6.20 (s, 1 H), 3.90-3.78 (m, 1H), 3.32-2.90 (m, 4H), 2.67 (s, 3H), 2.20-1.70 (m, 4H)

Following compounds are prepared analogously:

Example	Product
54	(3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxymethyl)biphenyl-3-yl]methanol, oxalate
	¹ H NMR (DMSO-d ⁶): 8.02 (d, 1H), 7.87 (d, 1H), 7.72 (s, 1H), 7.62-7.35 (m, 8H), 7.27 (d, 1H), 6.13 (s, 1H), 4.51 (s, 2H), 3.92-3.80 (m, 1H), 3.40-2.90 (m, 4H), 2.70 (s, 3H), 2.25-1.70 (m, 4H)
63	2-[(1-methylpiperidin-4-yloxy)(3-pyridin-3-ylphenyl)methyl]benzothiazole, oxalate
	¹ H NMR (DMSO-d ⁶): 8.86 (d, 1H), 8.57 (dd, 1H), 8.09-8.00 (m, 2H), 7.92 (d, 1H), 7.84 (s, 1H), 7.73-7.63 (m, 1H), 7.58-7.37 (m, 5H), 6.21 (s, 1H), 3.92-3.78 (m, 1H), 3.40-2.95 (m, 4H), 2.70 (s, 3H), 2.25-1.75 (m, 4H)
79	3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-ylamine, oxalate
	¹ H NMR (DMSO-d ⁶): 8.07 (d, 1H), 7.91 (d, 1H), 7.66 (s, 1H), 7.53-7.37 (m, 5H), 7.07 (t, 1H), 6.78 (s, 1H), 6.71 (d, 1H), 6.54 (d, 1H), 6.18 (s, 1H), 4.20-3.70 (m, 5H), 3.42-2.95 (m, 4H), 2.70 (s, 3H), 2.25-1.75 (m, 4H)
81	2-[biphenyl-3-yl(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
	¹ H NMR : 12.38 (sl, 1H), 7.78 (s, 1H), 7.65-7.40 (m, 10H), 7.15-7.05 (m, 2H), 5.91 (s, 1H), 3.50-3.35 (m, 1 H), 2.68-2.50 (m, 2H), 2.10 (s, 3H), 2.05-1.84 (m, 4H), 1.70-1.50 (m, 2H)
86	{3'-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-yl}methanol

¹ H NMR (DMSO-d ⁶): 12.37 (sl, 1H), 7.77 (s, 1H), 7.62-7.35 (m, 8H), 7.28 (d, 1H), 7.15-7.02 (m, 2H), 5.92 (s, 1H), 5.22 (t, 1H), 4.53 (d, 2H), 3.48-3.32 (m, 1H), 2.68-2.50 (m, 2H), 2.08 (s, 3H), 2.00-1.78 (m, 4H), 1.69-1.48 (m, 2H)	
87	3'-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-ylamine
¹ H NMR: 9.57 (sl, 1H), 7.82-8.68 (m, 1H), 7.67 (s, 1H), 7.55-7.35 (m, 4H), 7.30-7.15 (m, 3H), 6.94 (d, 1H), 6.85 (s, 1H), 6.67 (d, 1H), 5.92 (s, 1H), 3.85-3.50 (m, 3H), 2.80-2.75 (m, 2H), 2.27 (s, 3H), 2.25-1.65 (m, 6H)	
89	2-[(1-methylpiperidin-4-yloxy)(3-pyridin-3-ylphenyl)methyl]-1 <i>H</i> -benzimidazole
¹ H NMR: 9.62 (sl, 1H), 8.80 (d, 1H), 8.58 (dd, 1H), 7.83 (d, 1H), 7.80-7.65 (m, 2H), 7.55-7.20 (m, 7H), 5.96 (s, 1H), 3.70-3.55 (m, 1H), 2.85-2.70 (m, 2H), 2.30 (s, 3H), 2.25-1.65 (m, 6H)	
96	2-[(2'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
¹ H NMR: 8.02 (d, 1H), 7.88 (d, 1H), 7.74 (s, 1H), 7.55-7.25 (m, 7H), 7.08-6.95 (m, 2H), 5.99 (s, 1H), 3.77 (s, 3H), 3.75-3.65 (m, 1H), 2.82-2.68 (m, 2H), 2.29 (s, 3H), 2.29-2.15 (m, 2H), 2.10-1.80 (m, 4H)	
97	2-[(1-methylpiperidin-4-yloxy)(3'-nitrobiphenyl-3-yl)methyl]benzothiazole
¹ H NMR: 8.45 (d, 1H), 8.22 (d, 1H), 7.99 (d, 1H), 7.95-7.85 (m, 2H), 7.80 (s, 1H), 7.65-7.35 (m, 6H), 6.00 (s, 1H), 3.80-3.65 (m, 1H), 2.88-2.70 (m, 2H), 2.42-2.25 (m, 2H), 2.34 (s, 3H), 2.10-1.70 (m, 4H)	
99	2-[(3'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
¹ H NMR: 7.98 (d, 1H), 7.86 (d, 1H), 7.74 (s, 1H), 7.68-7.30 (m, 6H), 7.17 (d, 1H), 7.10 (d, 1H), 6.92 (d, 1H), 5.96 (s, 1H), 3.92-3.78 (m, 1H), 3.86 (s, 3H), 3.05-2.85 (m, 2H), 2.85-2.55 (m, 2H), 2.50 (s, 3H), 2.35-2.12 (m, 2H), 2.12-1.85 (m, 2H)	
100	2-[(4'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate
¹ H NMR: 8.06 (d, 1H), 7.91 (d, 1H), 7.71 (s, 1H), 7.50-7.30 (m, 7H), 7.02 (d, 2H), 6.18 (s, 1H), 3.92-3.78 (m, 1H), 3.77 (s, 3H), 3.45-2.90 (m, 4H), 2.70 (s, 3H), 2.12-1.72(m, 4H)	
128	2-[(1-methylpiperidin-4-yloxy)(3'-methylsulfanylbiphenyl-3-yl)methyl]benzothiazole, oxalate
¹ H NMR (DMSO d ⁶): 8.07 (d, 1H), 7.92 (d, 1H), 7.78 (s, 1H), 7.62 (sl, 1H), 7.55-7.32 (m, 7H), 7.27 (sl, 1H), 6.20 (s, 1H), 3.45-3.30 (m, 1H), 3.30-2.82 (m, 4H), 2.67 (s, 3H), 2.47 (s, 3H), 2.25-1.75 (m, 4H)	

133	2-[(3',4'-dichlorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
¹ H NMR: 7.98 (d, 1H), 7.88 (d, 1H), 7.70 (s, 1H), 7.66 (d, 1H), 7.52-7.35 (m, 7H), 5.97 (s, 1H), 3.82-3.68 (m, 1H), 2.95-2.78 (m, 2H), 2.55-2.40 (m, 2H), 2.40 (s, 3H), 2.20-1.80 (m, 4H)	
136	2-[(4'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
¹ H NMR: 7.98 (d, 1H), 7.86 (d, 1H), 7.71 (s, 1H), 7.68-7.30 (m, 7H), 7.15 (d, 1H), 7.10 (d, 1H), 5.98 (s, 1H), 3.80-3.63 (m, 1H), 2.88-2.72 (m, 2H), 2.42-2.25 (m, 2H), 2.34 (s, 3H), 2.15-1.75 (m, 4H)	
137	2-[(2'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
¹ H NMR: 7.99 (d, 1H), 7.88 (d, 1H), 7.75 (s, 1H), 7.50-7.10 (m, 9H), 5.98 (s, 1H), 3.82-3.75 (m, 1H), 2.88-2.70 (m, 2H), 2.33 (s, 3H), 2.40-2.20 (m, 2H), 2.12-1.85 (m, 4H)	

72 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

72A

5 A mixture of 1*H*-benzimidazol-2-yl(3-bromophenyl)methanol (12.9g), 4-hydroxy-1-methylpiperidine (4.86g) and para-toluenesulfonic acid (24g) in chlorobenzene (60mL) and *N*-methylpyrrolidone (6mL) is heated under reflux for 120h in a Dean Stark apparatus. Solvent is removed by evaporation. To the residue is added water which is made alkaline by addition of sodium hydroxyde solution, then extracted with ethyl acetate. The pooled
10 organic extracts are washed with water, treated with activated charcoal, dried over magnesium sulfate and concentrated under reduced pressure. The residue is triturated in diethyl ether to give 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole.

15 72B

A mixture of (3-bromophenyl)hydroxyacetic acid (20g) and ortho-phenylenediamine (9.36g) in 5N aqueous hydrochloric solution (100mL) is heated under reflux for 4h and cooled back to room temperature. The precipitate is separated by filtration, rinsed with acetonitrile and dried under vacuum with phosphorus pentoxyde et
20 give 1*H*-benzimidazol-2-yl(3-bromophenyl)methanol as a white crystalline solid used without further purification.

72C

To a solution of 3-bromobenzaldehyde (18.5g) in tetrahydrofuran (400mL) is added
25 trimethylsilylcyanide (10.9g). Two drops of a 1M solution of tetrabutylammonium fluoride

in tetrahydrofuran are added to the reaction mixture (a small exotherm is observed). After one hour at room temperature, solvent and volatiles are removed under reduced pressure. To the residual oil is added 6N aqueous hydrochloric acid (100mL). The round-bottom flask is equipped with a Dean-Stark apparatus and the reaction mixture is heated to reflux for 3 hours while removing silanols.

The reaction mixture is cooled to 0°C and a 10N sodium hydroxide solution is added dropwise to reach pH 1. The aqueous phase is extracted with ethyl acetate. The pooled organic phases are washed with brine; dried on magnesium sulphate and concentrated to dryness under reduced pressure. The residual solid is re-crystallized from hot toluene to give (3-bromophenyl)hydroxyacetic acid.

¹H NMR (DMSO-d⁶): 7.57 (t, 1H), (d, 1H), 7.45 (dt, 1H), 7.38 (s, 1H), 7.28 (t, 1H), 5.03 (s, 1H).

Following compounds are prepared using general methods 21A and 21B:

Example	Product
64	[(1 <i>H</i> -benzimidazol-2-yl)(3-bromophenyl)methyl](1-methylpiperidin-4-yl)amine
¹ H NMR: 9.60 (sl, 1H), 7.75 (sl, 1H), 7.65 (s, 1H), 7.50-7.32 (m, 3H), 7.30-7.15 (m, 3H), 5.84 (s, 1H), 3.62-3.58 (m, 1H), 2.85-2.68 (m, 2H), 2.28 (s, 3H), 2.25-1.65 (m, 7H)	

Example 56 : [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine enantiomer A

A solution of racemic [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine (10mg/mL) in a mixture of heptane / isopropanol (80 / 20) containing diethylamine (0.1%) is injected (20x100μL) onto an analytical Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (80 / 20) containing diethylamine (0.1%) at a flow of 1mL/min. Products are detected at 220nm.

The first enantiomer has a retention time of 6.7min.

Collection affords [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine enantiomer A with a chromatographic enantiomeric purity of 92.6%.

Example 57 : [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine enantiomer B

The second enantiomer has a retention time of 8.2min.

Collection affords [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine enantiomer B with a chromatographic enantiomeric purity of 98.8%.

Example 59 : [(1*H*-benzimidazol-2-yl)(3-trifluoromethylphenyl)methyl](1-methylpiperidin-4-yl)amine
5 59A

To a solution of (1*H*-benzimidazol-2-ylmethylene)(1-methylpiperidin-4-yl)amine (70mg) in tetrahydrofuran (3mL) is added a 1.5M solution of 3-trifluoromethylphenylmagnesium bromide in tetrahydrofuran (0.77mL) at room temperature. The
10 mixture is then stirred at 40°C for 1h, hydrolyzed with water and extracted with ethyl acetate. The pooled organic extracts are washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by column chromatography (gradient dichloromethane / methanol / ammonia from 95 / 5 / 0.5 to 90 / 10 / 0.5) to give [(1*H*-benzimidazol-2-yl)(3-trifluoromethylphenyl)methyl](1-methylpiperidin-
15 4-yl)amine as a yellow solid melting at 90°C.

59B

1*H*-Benzimidazole-2-carboxaldehyde (781 mg, can be prepared according to Fegy, K. Angewandte Chemie Int Ed, 1998, vol. 37, 1270-1273), 4-amino-1-methylpiperidine
20 (781mg) and 4Å molecular sieves (15g) in ethanol (100mL) are heated under reflux for 4h. The mixture is then filtered and the filtrate concentrated under reduced pressure to yield (1*H*-benzimidazol-2-ylmethylene)(1-methylpiperidin-4-yl)amine as a beige solid.

62

To a solution of 2-[(3-allyloxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (example 22) (2.35g) in tetrahydrofuran (40mL) is added tetrakis(triphenylphosphine)palladium (0.344g). The mixture is stirred for 5 min at room temperature, then sodium borohydride (0.576g) is added. The mixture is stirred for 20h at room temperature, filtered over a clarcel pad. The pad is rinsed with ethyl acetate. Pooled
30 organic phases are washed with aqueous ammonium chloride solution, then sodium hydrogenocarbonate, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by three column chromatographies over silica gel (twice gradient heptane / ethyl acetate from 95 / 5 to 80 / 20, third eluant heptane / dichloromethane 5 / 1). Pooled fractions are concentrated under reduced pressure. The
35 residue is dissolved in methanol, refluxed for 5h and concentrated under reduced pressure. The residue is purified by column chromatography (gradient dichloromethane /

methanol / ammonia from 100 / 0 to 90 / 10 / 1) to give 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenol as a beige solid melting at 201 °C.

* in the case of ketone-containing substituents, it is judicious to protect the carbonyl function (as an acetal for example) prior to the Grignard preparation

Example 91

91A

A mixture of 4-amino-1-methylpiperidine (0.23g), benzothiazol-2-yl(3-butoxyphenyl)methanol (0.63g), sodium hydrogenocarbonate (2mg) and dichloro(pentamethylcyclopentadienyl)iridium(III) dimer (8mg) in toluene (3mL) is heated in an autoclave at 110-120°C for 66 hours. The mixture is purified by chromatography over silica gel (eluant dichloromethane / methanol : 98 / 2) to give the crude base, which is transformed to the oxalate in acetone to give [benzothiazol-2-yl(3-butoxyphenyl)methyl](1-methylpiperidin-4-yl)amine oxalate melting at 176 °C.

91B

Benzothiazol-2-yl(3-butoxyphenyl)methanol can be obtained as described in example 1B.

Example 168

168A

2-[(1-methylpiperidin-4-yloxy)(3-pent-4-enyloxy-phenyl)methyl]benzothiazole, oxalate can be prepared as described in example 1A starting from benzothiazol-2-yl(3-pent-4-enyloxy-phenyl)methanol to get an orange solid melting at 75 °C.

168B

Benzothiazol-2-yl(3-pent-4-enyloxy-phenyl)methanol can be prepared as follows: to a 1M solution of 3-pent-4-enyloxy-phenylmagnesium bromide in tetrahydrofurane (2.2mL) diluted with the same solvent (6mL) cooled at -50 °C is added benzothiazole-2-carboxaldehyde (326mg). After stirring at -50 °C for 1h, the mixture is allowed to warm at room temperature, then hydrolyzed with aqueous saturated ammonium chloride solution and extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by column chromatography (gradient heptane / ethyl acetate from 4 / 1 to 2 / 1) to give benzothiazol-2-yl(3-pent-4-enyloxy-phenyl)methanol as a yellow oil.

272

2-[(1-methylpyrrolidin-3-yloxy)phenyl-methyl]-1*H*-benzimidazole

272A A mixture of (1*H*-benzimidazol-2-yl)phenylmethanol (611mg) and 1-methyl-3-pyrrolidinol (263mg) in methanesulfonic acid (1.3mL) is heated for 4 hours in a sealed tube at a temperature close to 140°C. The mixture is cooled back to room temperature, poored into water which is then made alkaline with concentrated sodium hydroxyde solution. The aqueous phase is extracted with ethyl acetate. Pooled extracts are dried over magnesium sulfate, concentrated under reduced pressure. The residue is purified by column chromatography over silica gel (gradient dichloromethane/methanol from 100/0 to 90/10) to give 2-[(1-methylpyrrolidin-3-yloxy)phenyl-methyl]-1*H*-benzimidazole melting at 53°C.

For the other examples prepared according this general procedure, it can be a good idea to rise the temperature progressively after having mixed the different reagents and to observe when etherification occurs. Once the right temperature has been found, reaction is continued up to adequate conversion.

272B

To a solution of 1-pyrrolidin-1-ylmethyl-1*H*-benzimidazole (5g) in tetrahydrofurane (20mL) cooled at a temperature close to -80°C, is added a 2.5M solution of butyl lithium in hexanes (10mL). The mixture is stirred for 15 minutes. A solution of benzaldehyde (2.64g) in tetrahydrofurane (20mL) is added. The mixture is stirred at a temperature close to -80°C for 1 hour, then at a temperature close to -20°C for 2 hours. The reaction is quenched by addition of saturated ammonium chloride. The mixture is extracted with ethyl acetate. Pooled extracts are washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by column chromatography over silica gel (gradient dichloromethane/methanol from 100/0 to 90/10) to give (1*H*-benzimidazol-2-yl)phenylmethanol used without further purification.

1-Pyrrolidin-1-ylmethyl-1*H*-benzimidazole can be prepared as described by Katritzky, Alan R.; Aslan, Diana C.; Leeming, Peter; Steel, Peter J. Tetrahedron: Asymmetry, 1997, 8, p. 1491 – 1500.

Example 370

370A

A mixture of 2-[3-(2-chloroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]-benzothiazole (625mg), potassium iodide (332mg), glycine *tert*-butyl ester, hydrochloride

(503mg) in triethylamine (630 μ L) and *N,N*-dimethylformamide (20mL) is heated overnight in a sealed tube at 70°C, then for 16h at 90-100°C. The mixture is cooled back to room temperature, poured into crushed ice and concentrated sodium hydroxide solution. The aqueous phase is extracted with ethyl acetate. The pooled organic phases are washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 90 / 10 / 1). The crude base is converted into its salt in acetone to give (2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamino)acetic acid *tert*-butyl ester, dioxalate melting at 136°C.

370B

2- [3-(2-chloroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole can be obtained as described in example 272A.

370C

benzothiazol-2-yl[3-(2-chloroethoxy)phenyl]methanol can be obtained as described in example 1B.

Example 371

371A

A mixture of 2-[[3-(5-azidopentyloxy)phenyl](1-methyl-piperidin-4-yloxy)methyl]benzothiazole (0.13g) and triphenylphosphine (0.11g) in a mixture of tetrahydrofurane (3mL) and water (2 drops) is heated at 70°C overnight. Solvent is removed under reduced pressure. The residue is dissolved in ethyl acetate and 0.5N hydrochloric solution. The aqueous phase is washed with ethyl acetate, made alkaline with concentrated sodium hydroxide solution and extracted with ethyl acetate. The pooled extracts are washed with saturated sodium chloride solution, dried over magnesium sulfate, concentrated under reduced pressure. The residue is purified by column chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 to 90 / 10 1) and salified with oxalic acid to give 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentyamine, oxalate melting at 141 °C.

371B

A mixture of 2-[[3-(5-chloropentyloxy)phenyl](1-methyl-piperidin-4-yloxy)-methyl]benzothiazole (200mg) and sodium azide (85mg) in dimethylsulfoxyde (3mL) is heated overnight at 70°C, then cooled back to room temperature. Water is added and the

product is extracted with ethyl acetate. Pooled extracts are washed with water, then brine, dried over magnesium sulfate and concentrated under reduced pressure to give 2-[[3-(5-azidopentyloxy)phenyl](1-methyl-piperidin-4-yloxy)methyl]benzothiazole used without further purification.

5

371C

2-[[3-(5-chloropentyloxy)phenyl](1-methyl-piperidin-4-yloxy)methyl]benzothiazole can be prepared according to the procedures described in examples 272A and 1B.

10

Further examples can be prepared according to the described general methods:

Example	Product	General methods	Melting point
55	2-[(3-isopropoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	68 °C
58	[benzothiazol-2-yl(1 <i>H</i> -pyrrol-2-yl)methyl](1-methylpiperidin-4-yl)amine	21A, 21B, 42C, 1B	125 °C
60	[(1 <i>H</i> -benzimidazol-2-yl)(3-trifluoromethoxyphenyl)-methyl](1-methylpiperidin-4-yl)amine	59A, 59B	82 °C
61	[(1 <i>H</i> -benzimidazol-2-yl)(3-ethylphenyl)methyl](1-methylpiperidin-4-yl)amine	59A, 59B	76 °C
65	[(1 <i>H</i> -benzimidazol-2-yl)(3-benzyloxyphenyl)-methyl](1-methylpiperidin-4-yl)amine	59A, 59B	78 °C
66	[(1 <i>H</i> -benzimidazol-2-yl)(3-isopropylphenyl)-methyl](1-methylpiperidin-4-yl)amine	59A, 59B	82 °C
67	[(1 <i>H</i> -benzimidazol-2-yl)(3-isobutoxyphenyl)-methyl](1-methylpiperidin-4-yl)amine	59A, 59B	99 °C
68	{(1 <i>H</i> -benzimidazol-2-yl)[3-(3-methylbutoxy)-phenyl]methyl}(1-methylpiperidin-4-yl)amine	59A, 59B	70 °C
69	[(1 <i>H</i> -benzimidazol-2-yl)(3-butoxyphenyl)methyl](1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	137 °C
70	[(1 <i>H</i> -benzimidazol-2-yl)(3-methoxyphenyl)-methyl](1-methylpiperidin-4-yl)amine	59A, 59B	182 °C
73	[(1 <i>H</i> -benzimidazol-2-yl)(3-cyclohexylmethoxy-phenyl)methyl](1-methylpiperidin-4-yl)amine	59A, 59B	88 °C

74	[(1 <i>H</i> -benzimidazol-2-yl)(3-fluorophenyl)methyl](1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	155 °C
75	[(1 <i>H</i> -benzimidazol-2-yl)(3-methylsulfanylphenyl)-methyl](1-methylpiperidin-4-yl)amine	59A, 59B	166 °C
76	[(1 <i>H</i> -benzimidazol-2-yl)(3-hexylphenyl)methyl](1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	115 °C
77	[(1 <i>H</i> -benzimidazol-2-yl)(3-isopropoxyphenyl)-methyl](1-methylpiperidin-4-yl)amine	59A, 59B	75 °C
83	[(1 <i>H</i> -benzimidazol-2-yl)(3-ethoxyphenyl)methyl](1-methylpiperidin-4-yl)amine	59A, 59B	74 °C
84	[(1 <i>H</i> -benzimidazol-2-yl)(<i>m</i> -tolyl)methyl](1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	132 °C
85	[(1 <i>H</i> -benzimidazol-2-yl)(3-phenoxyphenyl)-methyl](1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	144 °C
88	[benzothiazol-2-yl(3-isopropoxyphenyl)methyl](1-methylpiperidin-4-yl)amine, oxalate	21A, 21B, 21C, 1B 168B	96 °C
90	1-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-ylamino)methyl]phenyl}ethanone	59A, 59B *	198 °C
92	2-[(3-butoxyphenyl)(1-methylpiperidin-4-ylloxy)methyl]benzothiazole, oxalate	1A, 1B	135 °C
93	[benzothiazol-2-yl(3-cyclohexylmethoxyphenyl)-methyl](1-methylpiperidin-4-yl)amine, oxalate	21A, 37B, 42C, 1B 168B	98 °C
94	[(1 <i>H</i> -benzimidazol-2-yl)biphenyl-3-ylmethyl](1-methylpiperidin-4-yl)amine	59A, 59B	98 °C
95	[(1 <i>H</i> -benzimidazol-2-yl)(3-pentyloxyphenyl)-methyl](1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	128 °C
102	(benzothiazol-2-ylbiphenyl-3-ylmethyl)(1-methylpiperidin-4-yl)amine, oxalate	21A, 37B, 21C, 1B 168B	112 °C
103	{(1 <i>H</i> -benzimidazol-2-yl)[3-(4-fluorobenzyloxy)-phenyl]methyl}(1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	140 °C

104	[(1 <i>H</i> -benzimidazol-2-yl)(3-benzylsulfanylphenyl)-methyl](1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	127 °C
105	{(1 <i>H</i> -benzimidazol-2-yl)[3-(3-fluorobenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	116 °C
106	{(1 <i>H</i> -benzimidazol-2-yl)[3-(2-phenoxyethoxy)-phenyl]methyl}(1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	140 °C
107	[benzothiazol-2-yl(3-benzylsulfanylphenyl)-methyl](1-methylpiperidin-4-yl)amine, oxalate	91A 168B	50 °C
108	1-{3'-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-yl}ethanone, dioxalate	53	115 °C
109	2-[(3'-fluoro-biphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole, dioxalate	53	120 °C
110	1-{3'-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-yl}ethanone, dioxalate	53	140 °C
111	[benzothiazol-2-yl(3-methylsulfanylphenyl)-methyl](1-methylpiperidin-4-yl)amine, oxalate	91A 168B	85 °C
112	[(3-allyloxyphenyl)(1 <i>H</i> -benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	125 °C
113	{(1 <i>H</i> -benzimidazol-2-yl)[3-(2-fluorobenzyloxy)-phenyl]methyl}(1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	118 °C
114	2-[(1-methylpiperidin-4-yloxy)(2'-methylsulfanyl-biphenyl-3-yl)methyl]-1 <i>H</i> -benzimidazole	53	163 °C
115	2-[(4'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole, oxalate	53	100 °C
116	2-[(1-methylpiperidin-4-yloxy)(3'-methylsulfanyl-biphenyl-3-yl)methyl]-1 <i>H</i> -benzimidazole, dioxalate	53	80 °C
119	2-[(1-methylpiperidin-4-yloxy)(4'-trifluoromethyl-biphenyl-3-yl)methyl]-1 <i>H</i> -benzimidazole	53	95 °C
120	{(1 <i>H</i> -benzimidazol-2-yl)[3-(tetrahydropyran-2-yloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine	59A, 59B	97 °C
121	2-[(2'-Chlorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole, oxalate	53	130 °C

122	2-[(3',4'-dichlorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole, oxalate	53	150 °C
123	{3'-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-2-yl}methanol	53	107 °C
124	{(1 <i>H</i> -benzimidazol-2-yl)[3-(4-methoxybenzyloxy)-phenyl]methyl}(1-methylpiperidin-4-yl)amine	59A, 59B	84 °C
125	{(1 <i>H</i> -benzimidazol-2-yl)[3-(3-methoxybenzyloxy)-phenyl]methyl}(1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	135 °C
127	{3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-2-yl}methanol, oxalate	53	206- 207 °C
129	{(1 <i>H</i> -benzimidazol-2-yl)[3-(2-methylbenzyloxy)-phenyl]methyl}(1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	121 °C
130	{(1 <i>H</i> -benzimidazol-2-yl)[3-(4-methylbenzyloxy)-phenyl]methyl}(1-methylpiperidin-4-yl)amine	59A, 59B	87 °C
132	[(3-azidophenyl)(1 <i>H</i> -benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine	131, 231A, 231B	202 °C
138	{3'-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-yl}carbamic acid <i>tert</i> -butyl ester	53	135 °C
142	2-[(2'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	53	90 °C
144	[(1 <i>H</i> -benzimidazol-2-yl)(3-furan-2-ylphenyl)methyl](1-methylpiperidin-4-yl)amine	59A, 59B	108 °C
145	[(1 <i>H</i> -benzimidazol-2-yl)(3-but-3-enyloxyphenyl)-methyl](1-methylpiperidin-4-yl)amine	59A, 59B	71 °C
146	{(1 <i>H</i> -benzimidazol-2-yl)[3-(4-methylpentyloxy)-phenyl]methyl}(1-methylpiperidin-4-yl)amine	59A, 59B	73 °C
149	{(1 <i>H</i> -benzimidazol-2-yl)[3-(2,5-difluorobenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	159 °C
151	2-[(2-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	72A, 72B	212 °C

152	2-[(3-ethylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 168B	123 °C
155	2-[(3-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	72A, 72B, 72C	93 °C
161	2-[[3-(2,3-difluorobenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 168B	98 °C
162	{(1 <i>H</i> -benzimidazol-2-yl)[3-(2,3-difluorobenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine	59A, 59B	151 °C
163	2-[[3-(2-fluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 168B	147 °C
164	2-[(1-methylpiperidin-4-yloxy)(<i>m</i> -tolyl)methyl]-1 <i>H</i> -benzimidazole	72A, 72B, 72C	119 °C
166	5-fluoro-2-[(1-methylpiperidin-4-yloxy)phenylmethyl]-1 <i>H</i> -benzimidazole	165	134 °C
167	2-[(2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	72A, 72B, 72C	181 °C
169	2-[(1-methylpiperidin-4-yloxy)[3-(4,4,4-trifluorobutoxy)phenyl]methyl]benzothiazole, oxalate	1A, 168B	115 °C
170	5-bromo-2-[(1-methylpiperidin-4-yloxy)phenylmethyl]-1 <i>H</i> -benzimidazole	165	143 °C
171	2-[[3-(3-fluorobenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 168B	65 °C
174	((1 <i>H</i> -benzimidazol-2-yl)-{3-[3-(2-methyl-1,3)dioxolan-2-yl)-propoxy]phenyl)methyl}(1-methylpiperidin-4-yl)amine, oxalate	59A, 59B *	120 °C
175	{(1 <i>H</i> -benzimidazol-2-yl)[3-(4,4,4-trifluorobutoxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine	59A, 59B	94 °C
176	2-[[3-(3-fluoropropoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	72 °C
177	2-[(1-methylpiperidin-4-yloxy)- <i>p</i> -tolyl-methyl]-1 <i>H</i> -benzimidazole	72A, 72B, 72C	102 °C

179	2-[(4-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	72A, 72B, 72C	131 °C
180	{(1 <i>H</i> -benzimidazol-2-yl)[3-(2-fluoroethoxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	155 °C
181	((1 <i>H</i> -benzimidazol-2-yl)-{3-[2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethoxy]phenyl}methyl)(1-methylpiperidin-4-yl)amine, oxalate	59A, 59B	123 °C
182	2-[(1-methylpiperidin-4-yloxy)(4'-trifluoromethoxybiphenyl-3-yl)methyl]-1 <i>H</i> -benzimidazole	53	90 °C
183	2-[(4'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	53	92 °C
184	2-[(3-benzo[1,3]dioxol-5-ylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	53	95 °C
185	2-[[3-(3-methoxybenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 168B	77 °C
186	5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentan-2-one, oxalate	1A, 168B, *	72 °C
187	2-[(1-methylpiperidin-4-yloxy)[3-(3-trifluoromethylbenzyloxy)phenyl]methyl]benzothiazole, oxalate	1A, 168B	80 °C
190	3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-yn-1-ol	189	117-120 °C
191	4-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-yn-1-ol	189	104-108 °C
192	5-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-yn-1-ol	189	85 °C
193	2-[(1-methylpiperidin-4-yloxy)-o-tolyl-methyl]-1 <i>H</i> -benzimidazole	72A, 72B, 72C	190 °C
197	3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzonitrile, oxalate	72A, 1B	75 °C
204	2-[(4-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	72A, 72B, 72C	122 °C

213	2-[(2-chloro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole, oxalate	72A, 272B	96 °C
214	5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrimidin-2-ol	53	170 °C
216	2-[(1-methylpiperidin-4-yloxy)(3-pyrimidin-5-yl-phenyl)methyl]benzothiazole	53	85 °C
218	2-[(1-methylpiperidin-4-yloxy)(3-vinyl-phenyl)methyl]benzothiazole	217	165 °C
220	3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]- <i>N</i> -propylbenzamide	219	60 °C
221	2-[(2,4-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole, oxalate	72A, 272B	106 °C
222	[(1 <i>H</i> -benzimidazol-2-yl)(4'-methoxy-biphenyl-3-yl)methyl](1-methylpiperidin-4-yl)amine	21A, 37B, 211B, 42C, 272B	110 °C
223	3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]- <i>N</i> -methyl- <i>N</i> -phenylbenzamide, oxalate	219	125 °C
225	2-[(3-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole, oxalate	72A, 272B	158 °C
226	2-[(4-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole, oxalate	72A, 272B	175 °C
235	3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-3-methyl-butan-1-ol	150	80 °C
242	3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-3-methyl-butan-1-ol, oxalate	148	80 °C
243	2-[(1-methylpiperidin-4-yloxy)(3-morpholin-4-yl-phenyl)methyl]benzothiazole, oxalate	234	111 °C
244	2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethanol, oxalate	234	45 °C
246	3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-1-ol	150	97-99 °C

247	1-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-2-ol	150	120-122 °C
250	2-[(1-methylpiperidin-4-yloxy)[3-(2-methylsulfanylethoxy)phenyl]methyl}benzothiazole, oxalate	272A, 1B	89 °C
251	2-[(1-methylpiperidin-4-yloxy)(2-trifluoromethoxyphenyl)methyl]-1 <i>H</i> -benzimidazole	72A, 272B	193 °C
261	2-[(3-bromo-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	72A, 272B	92 °C
262	2-[(2-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	72A, 272B	213 °C
265	2-[(1-methylpiperidin-4-yloxy)[3-(pyridin-4-ylmethoxy)phenyl]methyl}benzothiazole, oxalate	258	101 °C
266	4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}butan-1-ol, oxalate	258	63 °C
267	2-[[3-(furan-2-ylmethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	258	85 °C
269	2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine, dioxalate	249, 149A	80 °C
271	2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamine	371A, 371B, 272A, 1B	76 °C
273	[(1 <i>H</i> -benzimidazol-2-yl)- <i>p</i> -tolyl-methyl](1-methylpiperidin-4-yl)amine	59A, 59C	183 °C
274	2-[(3-ethylsulfanyl-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole, oxalate	148, 272A, 272B	142 °C
277	2-[[3-(2-methoxyethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	80 °C
279	(2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)methyl-amine, dioxalate	258	125 °C
280	2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethoxyphenyl)methyl]-1 <i>H</i> -benzimidazole, oxalate	272A, 272B	172 °C
281	2-[(2-Chlorophenyl)(1-methylpiperidin-4-	272A, 1B	163 °C

	yloxy)methyl]benzothiazole, oxalate		
283	2-[(1-methylpiperidin-4-yloxy)[3-(pyridin-2-ylmethoxy)phenyl]methyl]benzothiazole, oxalate	272A, 1B	158 °C
284	2-[(1-methylpiperidin-4-yloxy)[3-(pyridin-3-ylmethoxy)phenyl]methyl]benzothiazole, oxalate	272A, 1B	102 °C
285	2-[(3-Cyclohexylmethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	101 °C
289	5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pentylamine, dihydrochloride	293, 194	110 °C
290	2-{3-[benzothiazol-2-yl(1-ethyl-piperidin-4-yloxy)methyl]phenoxy}ethylamine, dioxalate	371A, 371B, 272A, 1B	112 °C
291	2-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamine	371A, 371B, 272A, 272B	90 °C
292	6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexan-1-ol, oxalate	148	80 °C
300	2-[(2,3-dihydrobenzo[1,4]dioxin-6-yl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	272A, 272B	203 °C
302	<i>N</i> -(2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine, hydrochloride	278A, 249, 149A	125 °C
304	<i>N-tert</i> -butoxycarbonyl- <i>N'</i> -(2-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine	307A, 194A	110 °C
306	2-[(3-[2-(1-methyl-1 <i>H</i> -imidazol-4-yl)ethyl]phenyl)(1-methylpiperidin-4-yloxy)methyl]-benzothiazole, oxalate	293, 194	80 °C
310	2-[(1-methylpiperidin-4-yloxy)[3-(pyridin-2-ylmethoxy)phenyl]methyl]-1 <i>H</i> -benzimidazole	272A, 272B	77 °C
311	3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}propylamine, oxalate	371A, 371B, 272A, 1B	120 °C
314	3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propylamine, oxalate	305A, 305B	99 °C
319	6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine, oxalate	194, 189	135 °C

322	2-((1-methylpiperidin-4-yloxy)[3-(4-morpholin-4-yl-butoxy)phenyl]methyl)benzothiazole, oxalate	370A, 272A, 1B	61 °C
323	(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-2-yl)methanol, oxalate	258	76 °C
324	(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-2-yl)methanol, oxalate	258	99 °C
325	6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hexylamine, oxalate	293, 194	115 °C
326	4-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine, oxalate	305A, 305B	146 °C
327	3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}propylamine	371A, 371B, 272A, 272B	97 °C
329	4-(2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)piperazine-1-carboxylic acid <i>tert</i> -butyl ester, oxalate	370A, 272A; 1B	90 °C
331	4-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}butylamine, oxalate	371A, 371B, 272A, 272B	115 °C
332	2-((1-methylpiperidin-4-yloxy)[3-(4-morpholin-4-yl-butoxy)phenyl]methyl)-1 <i>H</i> -benzimidazole, oxalate	370A, 272A, 272B	85 °C
333	2-((1-methylpiperidin-4-yloxy)[3-(4-piperidin-1-yl-butoxy)phenyl]methyl)-1 <i>H</i> -benzimidazole, oxalate	370A, 272A, 272B	130 °C
334	2-[(2-fluoro-3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	272A, 272B	125 °C
339	<i>N</i> - <i>tert</i> -butoxycarbonyl- <i>N'</i> -(5-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-5-ynyl)guanidine	307A, 194A	125 °C
340	<i>N</i> -(5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)guanidine, hydrochloride		180 °C
341	<i>N</i> - <i>tert</i> -butoxycarbonyl- <i>N'</i> -(6-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine	307A, 194A	130 °C

342	<i>N</i> -(6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine, hydrochloride		185 °C
343	4-(4-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}butyl)piperazine-1-carboxylic acid <i>tert</i> -butyl ester	370A, 272A, 272B	64 °C
348	2-[(1-methylpiperidin-4-yloxy)[3-(3-[1,2,4]triazol-1-yl-propoxy)phenyl]methyl]benzothiazole, oxalate	315A, 272A, 1B	60 °C
349	2-[(1-methylpiperidin-4-yloxy)[3-(3-[1,2,3]triazol-2-yl-propoxy)phenyl]methyl]benzothiazole, oxalate (contains 23% of 1,2,3-triazol-1-yl compound)	315A, 272A, 1B	74 °C
350	2-[(1-methylpiperidin-4-yloxy)[3-(3-morpholin-4-yl-propoxy)phenyl]methyl]benzothiazole, oxalate	370A, 272A, 1B	105 °C
352	2-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluorophenylsulfanyl}ethylamine	423A, 150A, 272A, 272B	204 °C
354	2-[[3-(2-Chloroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	272A, 1B	70 °C
356	2-[(1-methylpiperidin-4-yloxy)[3-(2-piperidin-1-yl-ethoxy)phenyl]methyl]-1 <i>H</i> -benzimidazole, oxalate	370A, 272A, 272B	160 °C
360	4-(3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}propyl)piperazine-1-carboxylic acid <i>tert</i> -butyl ester, oxalate	370A, 272A, 272B	140 °C
362	4-(5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentyl)piperazine-1-carboxylic acid <i>tert</i> -butyl ester	370A, 272A, 1B	131 °C
363	<i>N</i> -(6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hexyl)guanidine, hydrochloride	278A, 249, 149A	90 °C
364	<i>N-tert</i> -butoxycarbonyl- <i>N'</i> -(6-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hexyl)guanidine	307A, 194A	90 °C
365	<i>N</i> -(5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pentyl)guanidine, hydrochloride	278A, 249, 149A	90 °C

366	4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}butylamine, dioxalate	293, 194	100 °C
367	[[3-(4-aminobutoxy)phenyl](1 <i>H</i> -benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine	21A, 37B, 371B, 42C, 272B	68 °C
368	3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propylamine	278A, 249, 149A	126 °C
369	4-(2-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)piperazine-1-carboxylic acid <i>tert</i> -butyl ester, dioxalate	370A, 272A; 1B	92 °C
373	<i>N</i> -(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)guanidine, trihydrochloride	278A, 249, 149A	125 °C
374	<i>N</i> -(4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}butyl)guanidine, trihydrochloride	278A, 249, 149A	120 °C
375	(5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentylamino)acetic acid <i>tert</i> -butyl ester, oxalate	370A, 272A, 1B	99 °C
377	2-[(1-methylpiperidin-4-yloxy)[3-(piperidin-4-ylmethoxy)phenyl]methyl}benzothiazole, dioxalate	423A, 258	90 °C
378	2-[(1-methylpiperidin-4-yloxy)[3-(piperidin-3-ylmethoxy)phenyl]methyl}benzothiazole, dioxalate	423A, 258	55 °C
379	2-[[3-(1-methylpiperidin-3-ylmethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, dioxalate	165C, 423A, 258	76 °C
380	2-[(1-methylpiperidin-4-yloxy)(3-piperidin-3-ylethynylphenyl)methyl]-1 <i>H</i> -benzimidazole	376A, 189	97 °C
381	5-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}pentylamine, oxalate	305A, 305B	140 °C
382	2-[(1-methylpiperidin-4-yloxy)[3-(pyrrolidin-3-yloxy)phenyl]methyl}benzothiazole, dioxalate	258	50 °C
387	{[3-(4-aminobutoxy)phenyl]benzothiazol-2-yl-methyl}(1-methylpiperidin-4-yl)amine	21A, 37B, 371B, 42C, 1B	67 °C

388	2-[(3-azetidin-3-ylethynylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	249, 293, 189	131 °C
389	5-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-en-1-ol, oxalate	384A, 53	125 °C
391	4-(5-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentyl)piperazine-1-carboxylic acid <i>tert</i> -butyl ester, dioxalate	370A, 72A, 272B	101 °C
392	2-[[3-(2-azetidin-3-ylethyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	249, 189	146 °C
395	2-[(1-methylpiperidin-4-yloxy)[3-(2-piperidin-2-ylethylsulfanyl)phenyl]methyl]-1 <i>H</i> -benzimidazole	249, 149A	164 °C
399	<i>N</i> - <i>tert</i> -butoxycarbonyl- <i>N'</i> -(4-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine	307A, 194A	120 °C
400	5-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentylamine, dioxalate	371A, 371B, 72A, 272B	111 °C
402	2-[[3-(azetidin-3-yloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, dioxalate	423A, 258	81 °C
404	(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)methanol, oxalate	403	106 °C
405	1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-ylamine, dioxalate	423A, 403	137 °C
406	1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ol, oxalate	403	103 °C
407	1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ol, oxalate	403	106 °C
408	<i>N</i> -(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)acetamide, oxalate	403	111 °C
410	2-[(1-methylpiperidin-4-yloxy)[3-(5-pyrazol-1-ylpent-1-ynyl)phenyl]methyl]-1 <i>H</i> -benzimidazole, oxalate	416A, 189	115 °C

413	acetic acid 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-yl ester, oxalate	403	74 °C
414	2-[(3-bromo-phenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]-1 <i>H</i> -benzimidazole	165C, 272A, 72B, 72C	61 °C
415	2-[(1-methylpiperidin-4-yloxy)[3-(piperidin-4-yloxy)phenyl]methyl]benzothiazole, dioxalate	423A, 258	76 °C
419	<i>N</i> 1-(5-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentyl)butane-1,4-diamine, dioxalate	423A, 370A, 72A, 272B	162 °C
420	{[3-(6-aminohex-1-ynyl)phenyl]benzothiazol-2-yl-methyl}(1-methylpiperidin-4-yl)amine, oxalate	386A, 275	80 °C
422	4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}but-2-en-1-ol, oxalate	258	73 °C
424	2-[(2,5-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	272A, 272B	140 °C
425	2-[(2-fluoro-5-iodo-phenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole, dioxalate	272A, 272B	175 °C
427	4-{3-[(5-fluoro-1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol	150	85 °C
428	2-{3-[(5-fluoro-1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-ethylamine, dioxalate	249, 149A	85 °C
429	1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ylamine, dioxalate	423A, 423B	137 °C
430	2-[[3-(3-fluoropyrrolidin-1-yl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	423B	70 °C
431	4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}but-2-enylamine, dioxalate	386A, 424A, 258	117 °C
433	2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	272A, 272B	95 °C

* in the case of ketone-containing substituents, it is judicious to protect the carbonyl function (as an acetal for example) prior to the Grignard preparation

Example 434

2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole enantiomer A

A solution of racemic 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole (1mg/mL) in a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) is injected (10μL) onto an analytical Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. Products are detected at 220nm.

The first enantiomer has a retention time of 6.9min.

Collection affords 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole enantiomer A with a chromatographic enantiomeric purity of 99.8%.

Example 435

2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole enantiomer B

The second enantiomer has a retention time of 8.3min.

Collection affords 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole enantiomer B with a chromatographic enantiomeric purity of 96.8%.

Following compounds are prepared using general methods described in example 1:

Example	Product
78	2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole
¹ H NMR: 9.62 (sl, 1H), 7.85-7.70 (m, 1H), 7.65 (s, 1H), 7.50-7.35 (m, 3H), 7.30-7.15 (m, 3H), 5.84 (s, 1H), 3.65-3.50 (m, 1H), 2.85-2.65 (m, 2H), 2.28 (s, 3H), 2.25-1.60 (m, 6H)	

80

2-[(3-butylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole

80A To a mixture of trifluoromethanesulfonic acid 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl ester (110mg) and ferric acetylacetonate (4mg) in a mixture of tetrahydrofurane (4.5mL) and *N*-methylpyrrolidone (0.25mL) cooled at 0°C is added a 2M solution of butylmagnesium chloride in tetrahydrofurane (150μL). The mixture is stirred at room temperature for 25 min, then warmed at 30°C for 15min. A second addition of butylmagnesium chloride in tetrahydrofurane (150μL) is performed. The

80

mixture is then diluted with diethyl ether and quenched with 0.5N hydrochloric solution. The aqueous phase is extracted with diethyl ether, then ethyl acetate. Organic phases are pooled, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient heptane / ethyl acetate from 99 / 1 to 90 / 10). The product is then refluxed in methanol and concentrated to give 2-[(3-butylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole.

TLC (eluent: CH₂Cl₂/MeOH 90/10): R_f= 0.30

80B

To a solution of 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenol (318mg) in pyridine (74μL) and dichloromethane (3mL) cooled at -5°C is added trifluoromethanesulfonic anhydride (152μL). The mixture is stirred for 1h, then allowed to warm to room temperature. The organic phase is washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient heptane / ethyl acetate from 95 / 5 to 50 / 50) to give trifluoromethanesulfonic acid 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl ester used without further purification.

Following compounds are prepared using general methods described in example 21A, 21C and 1B:

Example	Product
82	[benzothiazol-2-yl(3-bromophenyl)methyl](1-methylpiperidin-4-yl)amine
¹ H NMR (DMSO d ₆): 9.21 (sl, 1H), 8.02 (d, 1H), 7.85 (d, 1H), 7.52-7.20 (m, 6H), 5.39 (s, 1H), 3.45-3.30 (m, 1H), 3.05-2.80 (m, 2H), 2.75-2.55 (m, 2H), 2.65 (s, 3H), 2.25-1.85 (m, 2H), 1.80-1.45 (m, 2H)	

Example 117

2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole enantiomer A

A solution of racemic 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (10mg/mL) in a mixture of heptane / isopropanol (80 / 20) containing diethylamine (0.1%) is injected (20x100μL) onto an analytical Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (80 / 20) containing diethylamine (0.1%) at a flow of 1mL/min. Products are detected at 220nm.

The first enantiomer has a retention time of 6.0min.

Collection affords 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole enantiomer A with a chromatographic enantiomeric purity of 97.3%.

Example 118

2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole enantiomer B

The second enantiomer has a retention time of 7.0min.

Collection affords 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl] benzo-
5 thiazole enantiomer B with a chromatographic enantiomeric purity of 99.7%.

Example 126

3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-ylamino)methyl]phenol

A solution of {(1*H*-benzimidazol-2-yl)[3-(tetrahydropyran-2-yloxy)phenyl]methyl}(1-
10 methylpiperidin-4-yl)amine (example 120, 500mg) in ethanol (5mL) is treated with
aqueous 37% hydrochloric acid at room temperature for one night. The mixture is then
neutralized with an aqueous saturated sodium hydrogen carbonate solution and extracted
with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and
concentrated under reduced pressure. The residue is purified by column chromatography
15 (gradient dichloromethane / methanol / ammonia from 90 / 10 / 0.5 to 80 / 20 / 0.5) to give
3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-ylamino)methyl]phenol as a white solid
melting at 230 °C.

Example 131

20 [(1*H*-benzimidazol-2-yl)(3-nitrophenyl)methyl](1-methylpiperidin-4-yl)amine.

131A

To a solution of [(1*H*-benzimidazol-2-yl)(3-nitrophenyl)methylene](1-methyl-
piperidin-4-yl)amine (1.1g) in methanol (50mL) at 0 °C is added sodium cyanoborohydride,
then dropwise acetic acid (0.19mL). The reaction mixture is allowed to reach room
25 temperature and stirred at that temperature overnight.

Cold water (70mL) is added as well as concentrated hydrochloric acid to reach pH
1. Then a concentrated sodium hydroxide solution is added to reach pH 10. The aqueous
phase is extracted with dichloromethane. The pooled organic extracts are dried over
magnesium sulfate and concentrated under reduced pressure. The residue is purified by
30 chromatography (gradient dichloromethane / methanol from 99 / 1 to 95 / 5) to afford [(1*H*-
benzimidazol-2-yl)(3-nitrophenyl)methyl](1-methylpiperidin-4-yl)amine melting at 254 °C.

131B

[(1*H*-benzimidazol-2-yl)(3-nitrophenyl)methylene](1-methylpiperidin-4-yl)amine can
35 be prepared according to the method described in example 37B.

Further examples can be prepared according to the described general methods:

Example	Product	General methods	TLC
22	2-[(3-allyloxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, hydrochloride	1A, 1B	0.41(C)
32	2-[(2,3-dihydrobenzofuran-5-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 1B	0.32(C)
71	trifluoromethanesulfonic acid 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl ester	1A, 1B	0.50(D)
101	[benzothiazol-2-yl(3-benzyloxyphenyl)-methyl](1-methylpiperidin-4-yl)amine, oxalate	91A, 1B	0.17(C)
134	{(1 <i>H</i> -benzimidazol-2-yl)[3-(2-ethoxyethoxy)-phenyl]methyl}(1-methylpiperidin-4-yl)amine	59A, 59B	0.26(A)
135	[(1 <i>H</i> -benzimidazol-2-yl)(3-pent-4-enyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine	59A, 59B	0.16(A)
178	2-[(1-methylpiperidin-4-yloxy)[3-(3,3,3-trifluoro-propoxy)phenyl]methyl]-benzothiazole, oxalate	1A, 168B	0.67(D)
196	2-[(1-methylpiperidin-4-yloxy)[3-(3-nitro-benzyloxy)phenyl]methyl]benzothiazole, oxalate	1A, 1B	0,17(B)
270	1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzyloxy}propan-2-one, oxalate	1A, 168B *	0,32(A)
297	2-[benzo[1,3]dioxol-5-yl(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole	272A, 272B	0.22(D)
301	4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}butylamine, oxalate	371A, 371B, 272A, 1B	0,08(B)
328	4-(2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)piperazine-1-carboxylic acid <i>tert</i> -butyl ester	370A, 272A, 1B	0.69(D)

330	2-[(1-methylpiperidin-4-yloxy)[3-(2-piperazin-1-yl-ethoxy)phenyl]methyl]benzothiazole, oxalate	423A, 370A, 272A, 1B	0.26(D)
361	(2-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}-ethylamino)acetic acid <i>tert</i> -butyl ester, oxalate	370A, 272A, 1B	0.51(D)

Eluent A: CH₂Cl₂/MeOH/NH₄OH 90/10/0.5

Eluent B: CH₂Cl₂/MeOH/NH₄OH 95/5/0.5

Eluent C: CH₂Cl₂/MeOH 90/10

5 Eluent D: CH₂Cl₂/MeOH/NH₄OH 90/10/1

* in the case of ketone-containing substituents, it is judicious to protect the carbonyl function (as an acetal for example) prior to the Grignard preparation

Example 147

10 2-[(1-methylpiperidin-4-yloxy)(3-pyrazol-1-ylphenyl)methyl]benzothiazole, oxalate

To a solution of 2-[(3-Bromophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (208mg) in *N,N*-dimethylformamide (1mL) are added pyrazole (68mg), cesium carbonate (401mg) and copper(I) iodide (19mg). The tube is evacuated, filled with argon and sealed. After stirring at 120 °C for 48h, the mixture is diluted with water and ammonia solution then extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 95 / 5 / 0.5). The residue is added to a solution of oxalic acid (1 molar equivalent) and the residual precipitate is filtered and dried to afford 2-[(1-methylpiperidin-4-yloxy)(3-pyrazol-1-ylphenyl)methyl]benzothiazole oxalate melting at 89 °C.

Example 148

2-[(3-benzylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole.

A screw-cap tube is charged with 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (208mg), palladium bis(dibenzylideneacetone) (14mg), Xantphos (14mg), benzyl mercaptan (59μL), diisopropylethylamine (174μL) and 1,4-dioxane (2 mL). The tube is evacuated, filled with argon and sealed. After stirring at 120 °C for 15h, the mixture is diluted with ethyl acetate and water and the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium

sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 95 / 5 / 0.5). The residual yellowish oil is re-crystallized from hot acetonitrile to give 2-[(3-benzylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole melting at 195°C.

5

Further examples can be prepared according to the above described general method:

Example	Product
158	2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
	¹ H NMR: 7.98 (d, 1H), 7.88 (d, 1H), 7.57 (s, 1H), 7.47-7.27 (m, 5H), 5.88 (s, 1H), 3.75 (t, 2H), 3.65 (m, 1H), 3.12 (t, 2H), 2.70-2.81 (m, 2H), 2.30 (s, 3H), 1.7-2.4 (m, 7H)
159	2-[(3-ethylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
	¹ H NMR: 7.98 (d, 1H), 7.88 (d, 1H), 7.50-7.30 (m, 3H), 7.30-7.10 (m, 3H), 5.83 (s, 1H), 3.93 (m, 1H), 3.25-3.00 (m, 4H), 2.95 (q, 2H), 2.67 (s, 3H), 2.50-2.30 (m, 2H), 2.20-2.00 (m, 2H), 1.30(t, 3H)
160	{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid methyl ester
	¹ H NMR: 7.98 (d, 1H), 7.87 (d, 1H), 7.62 (s, 1H), 7.50-7.29 (m, 5H), 5.85 (s, 1H), 4.02 (s, 1H), 3.74-3.65 (m, 5H), 3.4-3.2 (m, 4H), 2.79 (s, 3H), 2.6-2.4 (m, 2H), 2.25-2.05 (m, 2H)
201	2-[(1-methylpiperidin-4-yloxy)(3-methylsulfanyl-phenyl)methyl]benzothiazole
	¹ H NMR: 7.97 (d, 1H), 7.87 (d, 1H), 7.50-7.10 (m, 6H), 5.89 (s, 1H), 3.70-3.58 (m, 1H), 2.62-2.78 (m, 2H), 2.48 (s, 3H) 2.23 (s, 3H), 2.23-2.10 (m, 2H), 2.00-1.7 (m, 4H)
233	2-[(1-methylpiperidin-4-yloxy)[3-(2-pyrazin-2-ylethylsulfanyl)phenyl]methyl]benzothiazole
	¹ H NMR: 8.47 (m, 1H), 8.40 (m, 1H), 7.96 (d, 1H), 7.85 (d, 1H), 7.53 (s, 1H), 7.45-7.27 (m, 6H), 5.88 (s, 1H), 3.8-3.60 (m, 1H), 3.34 (t, 2H), 3.09 (t, 2H), 2.82-2.75 (m, 2H), 2.34 (s, 3H), 2.50-2.20 (m, 2H), 2.1-1.70 (m, 4H)
239	(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-cyclopropyl)acetic acid methyl ester
	¹ H NMR: 7.97 (d, 1H), 7.87 (d, 1H), 7.53 (s, 1H), 7.48-7.24 (m, 5H), 5.87 (s, 1H), 3.7-3.5 (m, 4H), 3.08 (s, 2H), 2.80-2.65 (m, 2H), 2.46 (s, 2H), 2.30 (s, 3H), 2.32-2.2 (m, 2H), 2.10-1.75 (m, 4H), 0.50 (m, 4H)
254	3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-1-ol

Example	Product
	¹ H NMR: 7.96 (d, 1H), 7.87 (d, 1H), 7.57 (s, 1H), 7.46-7.24 (m, 5H), 5.88 (s, 1H), 3.8-3.65 (m, 3H), 3.28-3.15 (m, 1H), 3.07-2.97 (m, 1H), 2.87-2.70 (m, 2H), 2.34 (s, 3H), 2.45-2.25 (m, 2H), 2.20-1.75 (m, 7H)
255	1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-2-ol
	¹ H NMR: 8.06 (d, 1H), 7.91 (d, 1H), 7.46-7.24 (m, 6H), 6.09 (s, 1H), 5.5-4.0 (sl, 1H), 3.85-3.70 (m, 2H), 3.28-3.07 (m, 2H), 3.07-2.85 (m, 4H), 2.63 (s, 3H), 2.18-1.70 (m, 4H), 1.11 (d, 3H)
256	4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol
	¹ H NMR: 7.97 (d, 1H), 7.87 (d, 1H), 7.50-7.24 (m, 6H), 5.88 (s, 1H), 3.77-3.60 (m, 3H), 3.00-2.90 (m, 2H), 2.85-2.70 (m, 2H), 2.33 (s, 3H), 2.41-2.20 (m, 2H), 2.20-1.60 (m, 9H)

Example 1502-[(3-benzylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

5

A screw-cap tube is charged with 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole (200mg), palladium bis(dibenzylideneacetone) (14mg), Xantphos (14mg), benzyl mercaptan (59μL), Diisopropylethylamine (174μL) and 1,4-dioxane (2mL). The tube is evacuated, filled with argon and sealed. After stirring at 120°C for 24h, the mixture is diluted with ethyl acetate and water and the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 95 / 5 / 0.5) to afford 2-[(3-benzylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

15

¹H NMR: 12.38 (sl, 1H), 7.55 (d, 1H), 7.50-7.40 (m, 2H), 7.30-7.00 (m, 10H), 5.84 (s, 1H), 4.20 (s, 2H), 3.65-3.45 (m, 1H), 3.20-3.00 (m, 2H), 2.90-2.60 (m, 2H), 2.57 (s, 3H), 2.00-1.60 (m, 4H)

20

Further examples can be prepared according to the above described general method:

Example	Product
153	2-[(3-ethylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole
	¹ H NMR: 7.54 (sl, 1H), 7.40 (s, 1H), 7.27-7.17 (m, 6H), 5.82 (s, 1H), 3.65-3.50 (m, 1H), 2.87 (q, 2H), 2.80-2.60 (m, 2H), 2.23 (s, 3H), 2.20-1.65 (m, 6H), 1.23 (s, 3H)
154	{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid methyl ester
	¹ H NMR: 9.66 (sl, 1H), 7.90-7.20 (m, 8H), 5.84 (s, 1H), 3.71-3.50 (m, 6H), 2.80-2.60 (m, 2H), 2.28 (s, 3H), 2.27-1.65 (m, 6H)
157	2-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
	¹ H NMR: 9.76 (sl, 1H), 7.72 (s, 1H), 7.52 (s, 1H), 7.42 (s, 1H), 7.30-7.15 (m, 5H), 5.84 (s, 1H), 3.74 (t, 2H), 3.57-3.51 (m, 1H), 3.10 (t, 2H), 2.75-2.55 (m, 2H), 2.24 (s, 3H), 2.10-1.60 (m, 7H)
173	2-[[3-(furan-2-ylmethylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole
	¹ H NMR: 12.36 (sl, 1H), 7.54-7.44 (m, 4H), 7.26 (m, 3H), 7.18-7.10 (m, 2H), 6.22-6.15 (m, 2H), 5.83 (s, 1H), 4.20 (s, 2H), 3.35-3.50 (m, 1H), 3.0-2.8 (m, 2H), 2.36 (s, 3H), 2.0-1.8 (m, 2H), 1.8-1.6 (m, 2H), 1.25-1.05 (m, 2H)
202	2-[(1-methylpiperidin-4-yloxy)(3-methylsulfanyl-phenyl)methyl]-1 <i>H</i> -benzimidazole
	¹ H NMR: 7.65-7.52 (m, 2H), 7.36 (s, 1H), 7.30-7.10 (m, 5H), 5.85 (s, 1H), 3.97-3.85 (m, 1H), 3.47-3.30 (m, 2H), 3.20-2.90 (m, 2H), 2.69 (s, 3H), 2.43 (s, 3H), 2.38-2.0 (m, 4H)
215	2-[(3- <i>tert</i> -butylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole
	¹ H NMR: 9.51 (sl, 1H), 7.67 (s, 1H), 7.55-7.40 (m, 4H), 7.38-7.20 (m, 3H), 5.88 (s, 1H), 3.70-3.55 (m, 1H), 2.85-2.70 (m, 2H), 2.29 (s, 3H), 2.28-2.10 (m, 2H), 2.05-1.70 (m, 4H), 1.25 (s, 9H)
232	2-[(1-methylpiperidin-4-yloxy)[3-(2-pyrazin-2-yl-ethylsulfanyl)phenyl]methyl]-1 <i>H</i> -benzimidazole
	¹ H NMR: 10.24 (sl, 1H), 8.48 (m, 1H), 8.41 (m, 2H), 7.73 (sl, 1H), 7.51 (s, 1H), 7.33 (sl, 1H), 7.27-7.15 (m, 5H), 5.85 (s, 1H), 3.70-3.60 (m, 1H), 3.34 (t, 2H), 3.09 (t, 2H), 1.60-1.80 (m, 2H), 2.23 (s, 3H), 2.23-1.60 (m, 6H)
248	4-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol

¹ H NMR: 10.04 (sl, 1H), 7.88-7.35 (m, 3H), 7.30-7.15 (m, 5H), 5.83 (s, 1H), 3.75-3.62 (m, 2H), 3.62-3.58 (m, 1H), 2.92 (t, 2H), 2.85-2.65 (m, 2H), 2.27 (s, 3H), 2.20-2.05 (m, 2H), 2.05-1.6 (m, 9H)	
288	3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propane-1,2-diol
¹ H NMR: 12.38 (sl, 1H), 7.52 (d, 1H), 7.40-7.40 (m, 2H) 7.30-7.04 (m, 5H), 5.83 (s, 1H), 5.00-4.3 (m, 3H), 3.80-4.10 (m, 4H), 2.90-2.70 (m, 2H), 2.50-2.33 (m, 1H), 2.33 (s, 3H), 2.00-1.80 (m, 2H), 1.70-1.50 (m, 2H)	
295	6-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexan-1-ol
¹ H NMR: 10.08 (sl, 1H), 7.85-7.60 (m, 1H), 7.43 (sl, 2H), 7.32-7.15 (m, 5H), 5.84 (s, 1H), 3.70-3.50 (m, 3H), 2.92 -2.65 (m, 4H), 2.28 (s, 3H), 2.20-1.30 (m, 14H)	

Example 165

165A

5 5,6-dichloro-2-[(1-methylpiperidin-4-yloxy)phenylmethyl]-1*H*-benzimidazole

A round-bottom flask is charged with 4,5-dichlorobenzene-1,2-diamine (354mg) and toluene (2mL); a solution of trimethylaluminum 2M in toluene (1mL) is added dropwise. The reaction mixture is heated at 60°C for one hour. A solution of (1-methylpiperidin-4-yloxy)phenylacetic acid ethyl ester in toluene (1mL) is added dropwise and heating is pursued for one hour. The reaction mixture is cooled to room-temperature and a solution of sodium hydroxide is added dropwise to pH 10. The slurry is filtered on celite, cake washed with water (4x5mL) and ethyl acetate (4x5mL). After decantation, the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is diluted with glacial acetic acid (3mL) and the reaction mixture is heated at reflux for one hour. Acetic acid is removed on a rotary evaporator and the residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0 to 95 / 5 / 0.5 to give 5,6-dichloro-2-[(1-methylpiperidin-4-yloxy)phenylmethyl]-1*H*-benzimidazole melting at 221 °C.

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165B (1-Methylpiperidin-4-yloxy)phenylacetic acid ethyl ester.

To a solution of 4-(Ethoxycarbonyl-phenyl-methoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (3.4g) in dichloromethane (25mL) is added trifluoroacetic acid (18mL). After 30 minutes at room temperature, the volatiles are removed under reduced pressure.

Water (30mL) is added and the solution is basified by adding a solution of saturated sodium carbonate to pH 10. The aqueous phase is extracted with dichloromethane. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure to give (1-methylpiperidin-4-yloxy)phenylacetic acid ethyl ester used without further purification.

165C

(1-Methylpiperidin-4-yloxy)phenylacetic acid ethyl ester obtained above is dissolved in 1,4-dioxane (40mL) and 40% aqueous solution of formaldehyde (4mL) as well as a 1molar solution of sodium hypophosphorous acid (46mL); The reaction mixture is heated to 80°C overnight. 1,4-dioxane is removed under reduced pressure and the residual solution is basified by adding a solution of saturated sodium carbonate to pH 10. The aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 95 / 5 / 0.5) to afford (1-methylpiperidin-4-yloxy)phenylacetic acid ethyl ester.

¹H NMR: 7.50-7.45 (m, 2H), 7.38-7.20 (m, 3H), 5.00 (s, 1H), 4.18 (q, 2H), 3.55-3.40 (m, 1H), 2.83-2.65 (m, 2H), 2.28 (s, 3H), 2.25-2.08 (m, 2H), 2.05-1.65 (m, 4H), 1.22 (t, 3H)

165D 4-(Ethoxycarbonylphenylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of diazophenylacetic acid ethyl ester (2.55g) in 1,2-dichloroethane is added 4-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester (5.4g). The flask is evacuated and filled with argon. Rhodium(II) acetate-dimer (60mg) is added to the reaction mixture. Evolution of nitrogen occurs until the end of the reaction (about 1 hour). The solvent is removed under reduced pressure. The residue is purified by chromatography (gradient heptane / ethyl acetate from 95 / 5 to 80 / 20) to give 4-(ethoxycarbonylphenylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester.

¹H NMR: 7.52-7.28 (m, 5H), 5.01 (s, 1H), 4.15 (q, 2H), 3.90-3.70 (m, 2H), 3.68-3.55 (m, 1H), 3.18-3.00 (m, 2H), 2.00-1.50 (m, 4H), 1.44 (s, 9H), 1.26 (t, 3H)

165E Diazophenylacetic acid ethyl ester

To a solution of ethyl phenylacetate (3.28g) in acetonitrile (60mL) is added paratoluenesulfonylazide (4.53g). The reaction mixture is cooled to 0°C and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.9mL) is added dropwise. The reaction mixture is kept at 5°C overnight. Solvent is removed to dryness and the residue is purified by

chromatography (gradient petroleum ether / dichloromethane from 90 / 10 to 80 / 20) to give diazophenylacetic acid ethyl ester;

¹H NMR: 7.48-7.58 (m, 2H), 7.45-7.30 (m, 2H), 7.22-7.10 (m, 1H), 4.35 (q, 2H), 1.30 (t, 3H)

5

Example 172

3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzonitrile

To a solution of 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (200mg) in *N,N*-dimethylformamide (2.5mL) and water (0.2mL) are added
10 copper(I) cyanide (180mg), bis(dibenzylidenacetone)palladium (14.3mg) and Xantphos (14.4mg). The tube is evacuated, filled with argon and sealed. After stirring at 120°C for 48h, the mixture is diluted with water then extracted with ethyl acetate. The pooled organic extracts are washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient
15 dichloromethane / methanol / ammonia from 100 / 0 / 0 to 92.5 / 7.5 / 0.75) to afford 3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzonitrile

¹H NMR: 9.75 (s, 1H), 7.82 (s, 1H), 7.80-7.62 (m, 2H), 7.57 (d, 1H), 7.50-7.20 (m, 4H), 5.89 (s, 1H), 3.60-3.40 (m, 1H), 2.75-2.55 (m, 2H), 2.25 (s, 3H), 2.20-1.60 (m, 6H)

20

Example 188

4-[benzothiazol-2-yl(3-bromo-phenyl)methoxy]-1,1-dimethylpiperidinium

To a solution of 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (100mg) in acetonitrile is added iodomethane (1 molar equivalent) and the reaction mixture is refluxed for 1 hour. Solvent is removed under reduced pressure to
25 dryness, the residue is triturated with diethylether, filtered, the cake is washed with diethylether and dried to give 4-[benzothiazol-2-yl(3-bromo-phenyl)methoxy]-1,1-dimethylpiperidinium melting at 95 °C.

Example 189

30 2-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)isoindole-1,3-dione

A screw-cap tube is charged with 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole (200 mg), dichloro-bis(triphenylphosphine) palladium(II) (9.2 mg), copper(I) iodide (16.4 mg), *N*-propargylphthalimide (400 mg), diethylamine (310μL) and *N,N*-dimethylformamide (2 mL). The tube is evacuated, filled with argon and
35 sealed. After stirring at room-temperature for 24h, the mixture is diluted with water and the

aqueous phase is extracted with ethyl acetate. The pooled organic extracts are washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 95 / 5 / 0.5 to give 2-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)isoindole-1,3-dione.

¹H NMR: 9.52 (sl, 1H), 7.91-7.15 (m, 12H), 5.81 (s, 1H), 4.66 (s, 2H), 3.65-3.55 (m, 1H), 2.85-2.65 (m, 2H), 2.28 (s, 3H), 2.30-2.05 (m, 2H), 2.05-1.60 (m, 4H)

Following compounds are prepared analogously:

Example	Product
227	3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-yn-1-ol
	¹ H NMR: 7.96 (d, 1H), 7.85 (d, 1H), 7.51 (s, 1H), 7.55-7.23 (m, 5H), 5.89 (s, 1H), 4.46 (s, 2H), 3.70-3.55 (m, 1H), 2.78-2.62 (m, 2H), 2.27 (s, 3H), 2.27-2.08 (m, 2H), 2.05-1.70 (m, 4H)
236	4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-yn-1-ol
	¹ H NMR: 7.97 (d, 1H), 7.87 (d, 1H), 7.58 (s, 1H), 7.47-7.27 (m, 5H), 5.87 (s, 1H), 3.88-3.65 (m, 3H), 2.95-2.80 (m, 2H), 2.67 (t, 2H), 2.39 (s, 3H), 2.45-2.30 (m, 2H), 2.18 (s, 1H), 2.17-1.80 (m, 4H)
237	5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-yn-1-ol hydrochloride
	¹ H NMR (DMSO-d ⁶): 9.79 (sl, 1H), 8.07 (d, 1H), 7.92 (d, 1H), 7.50-7.30 (m, 5H), 6.12 (d, 1H), 3.92-3.70 (m, 1H), 3.50-2.95 (m, 6H), 2.76 and 2.67 (d, 3H), 2.48-2.35 (m, 2H), 2.30-1.60 (m, 6H)

Example 194

3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynylamine

194A

A solution of 2-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)isoindole-1,3-dione (70mg) and hydrazine hydrate (70μL) in ethanol (0.7mL) is stirred at room temperature for 3 hours. Ethanol is removed under reduced pressure and 1N hydrochloric acid in water is added to the organic residue and stirred for 5 minutes. The mixture is filtered, cake washed with ethyl acetate. The filtrate is extracted

by dichloromethane. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue purified by chromatography (dichloromethane / methanol / ammonia from 90 / 10 / 1) to afford 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynylamine melting at 101 °C

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194B

2-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)isoindole-1,3-dione is prepared according to general procedure 189.

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Following compounds are prepared analogously:

Example	Product
282	4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynylamine ¹ H NMR: 7.98 (d, 1H), 7.88 (d, 1H), 7.58 (s, 1H), 7.52-7.25 (m, 5H), 5.86 (s, 1H), 3.82-3.68 (m, 1H), 2.95-2.70 (m, 2H), 2.68-2.50 (m, 4H), 2.47 (s, 3H), 2.40-1.75 (m, 6H)
286	4-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynylamine ¹ H NMR: 9.50 (sl, 1H), 7.72 (sl, 1H), 7.55-7.20 (m, 7H), 5.84 (s, 1H), 3.65-3.55 (m, 1H), 2.91 (t, 2H), 2.80-2.65 (m, 2H), 2.54 (t, 2H), 2.26 (s, 3H), 2.18-1.60 (m, 6H)
287	e5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine ¹ H NMR: 7.97 (d, 1H), 7.87 (d, 1H), 7.56 (s, 1H), 7.46-7.24 (m, 5H), 5.87 (s, 1H), 3.71-3.56 (m, 1H), 2.95-2.82 (m, 2H), 2.82-2.66 (m, 2H), 2.47 (t, 2H), 2.29 (s, 3H), 2.28-2.18 (m, 2H), 2.10-1.70 (m, 8H)
337	6-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine ¹ H NMR: 7.70-7.45 (m, 3H), 7.40-7.10 (m, 5H), 5.84 (s, 1H), 3.60-3.55 (m, 2H), 3.32-3.17 (m, 1H), 2.80-2.60 (m, 4H), 2.45-2.30 (m, 2H), 2.24 (s, 3H), 2.18-1.50 (m, 10H)

Example 195

2-[(3-ethynylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

195A

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To a solution of 2-[(3-trimethylsilylethynylphenyl)(1-methylpiperidin-4-yloxy)-methyl]-1*H*-benzimidazole (205mg) in methanol (2mL) is added potassium carbonate (81mg). The reaction mixture is stirred at room temperature for 4 hours, then methanol is removed under reduced pressure. The residue is dissolved in water and extracted with

ethyl acetate. The organic phase is dried on magnesium sulphate and solvent is removed under reduced pressure to give 2-[(3-ethynylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

¹H NMR: 9.42 (sl, 1H), 7.80-7.70 (m, 1H), 7.62 (s, 1H), 7.48-7.36 (m, 3H) 7.34-7.20 (m, 3H), 5.86 (s, 1H), 3.65-3.48 (m, 1H), 3.07 (s, 1H), 2.78-2.65 (m, 2H), 2.25 (s, 3H), 2.20-1.60 (m, 6H)

195B

2-[(3-trimethylsilylethynylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole can be obtained using general method described in example 189.

Example 198

2-[(1-methylpiperidin-4-yloxy)[3-(1*H*-[1,2,3]triazol-4-yl)phenyl]methyl]-1*H*-benzimidazole

To a solution of 2-[(3-(ethynylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole (110mg) in methanol (2mL) and *N,N*-dimethylformamide (0.7mL) in a screw-cap tube is added L). The reaction mixture + copper(I) iodide (3.2mg) and azidotrimethylsilane (56 is heated at 100°C overnight, then solvents are removed under reduced pressure. The residue is dissolved in water and ammonia solution is added to pH10 ; the aqueous phase is extracted with dichloromethane. The organic phase is dried on magnesium sulphate and solvent is removed under reduced pressure to give 2-[(1-methylpiperidin-4-yloxy)[3-(1*H*-[1,2,3]triazol-4-yl)phenyl]methyl]-1*H*-benzimidazole.

¹H NMR: 7.98 (s, 1H), 7.86 (s, 1H), 7.80-7.50 (m, 3H), 7.48-7.30 (m, 2H), 7.29-7.15 (m, 2H), 5.95 (s, 1H), 3.68-3.50 (m, 1H), 2.96-2.89 (m, 1H), 2.85-2.65 (m, 2H), 2.26 (s, 3H), 2.20-1.70 (m, 6H)

Example 199

3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzoic acid methyl ester, oxalate

A solution of 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzonitrile (109 mg, example 197) in methanol (5mL) is treated with a flow of hydrogen chloride while refluxing for 4h. After stirring at room temperature for one night, the mixture is concentrated under reduced pressure and the residue purified over silica gel (dichloromethane / methanol / ammonia 95 / 5 / 0.5) to afford 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzoic acid methyl ester which is then converted into its oxalate salt in acetone to give 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzoic acid methyl ester, oxalate melting at 93°C.

Example 200

2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-3*H*-benzimidazol-4-ylamine

To a solution of DMF (44mg) in L). As soon as □1,2-dichloroethane (2.5mL) is added dropwise oxalylchloride (51 the gas evolution ceased, the volatiles are removed under reduced pressure. To the residue are added 1,2-dichloroethane (2.5mL) and (1-methylpiperidin-4-yloxy)phenylacetic acid (125mg). The reaction mixture is stirred at room temperature for 1 hour, then 1,2-diamino-3-nitrobenzene is added and the mixture is stirred overnight. Water is added and the solution is basified by adding a solution of saturated sodium carbonate to pH 10. The aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 95 / 5 / 0.5).

To the residual solid in ethanol (4.5mL) is added tin(II)dichloride. The reaction mixture is refluxed for 2 hours. The solution is basified by adding a solution of 10N sodium hydroxide to pH 6. The aqueous phase is extracted with chloroform. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is dissolved in acetic acid and the reaction mixture is refluxed for 3 hours. Acetic acid is removed, methanol (1mL) and 12N hydrochloric acid are added to the residue. The reaction mixture is heated to 60°C for 1 hour.

The solution is basified by adding a solution of saturated sodium carbonate to pH 10. The aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1) to afford 2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-3*H*-benzimidazol-4-ylamine melting at 96,7°C.

Example 203

2-[(3-methanesulfonylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole

To a solution of 2-[(1-methylpiperidin-4-yloxy)(3-methylsulfanylphenyl) methyl]-benzothiazole (100mg) in methanol (2mL) and water (1mL) at 0°C is added portionwise Oxone® (400mg) over 1hour.

The mixture is diluted with water. The aqueous phase is extracted with ethyl acetate. The pooled organic extracts are washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol from 98 / 2 to 90 / 10) to afford 2-[(3-methanesulfonylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole.

¹H NMR: 8.17 (s, 1H), 7.97 (d, 1H), 7.90-7.83 (m, 3H), 7.60-7.39 (m, 3H), 6.00 (s, 1H), 3.72-3.60 (m, 1H), 3.06 (s, 3H), 2.82-2.75 (m, 2H), 2.28 (s, 3H), 2.28-2.10 (m, 2H), 2.05-1.70 (m, 4H)

5 Example 206

3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzoic acid ethyl ester, oxalate

3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzoic acid ethyl ester, oxalate melting at 104°C can be prepared as described in example 199.

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Example 207

{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}methanol, oxalate

A solution of 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzoic acid ethyl ester (0.55g, example 206) in tetrahydrofuran (10mL) is treated with lithium aluminum hydride (76mg) at room temperature for 1h. Two other additions of lithium aluminum hydride (76mg each) allow a complete conversion. The mixture is then hydrolyzed with water (178μL), 5% sodium hydroxide (178μL) and water (535μL), filtered through a pad of clarcel and concentrated under reduced pressure. The residue is purified over silica gel (dichloromethane / methanol / ammonia 95 / 5 / 0.5) to afford {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}methanol which is then converted into its oxalate salt in acetone to give {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}methanol, oxalate.

20

¹H NMR (DMSO-d₆): 8.06 (d, 1H), 7.90 (d, 1H), 7.50-7.20 (m, 6H), 6.09 (s, 1H), 4.47 (s, 2H), 3.75 (m, 1H), 3.16 (m, 2H), 2.98 (m, 2H), 2.64 (s, 3H), 2.10-1.75 (m, 4H).

25

Example 208

3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}propionic acid *tert*-butyl ester

A screw-cap tube is charged with 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (208mg), palladium(II) acetate (3mg), RuPhos ® (12mg), potassium 3-trifluoroboropropionate *tert*-butyl ester (118mg), potassium carbonate (207 mg), water (2.5 mL) and toluene (2.5 mL). The tube is evacuated, filled with argon and sealed. After stirring at 120°C overnight, the mixture is diluted with ethyl acetate and water and the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol from 100 / 0 to 95 / 5) to

30

35

afford 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}propionic acid *tert*-butyl ester.

¹H NMR : 7.97 (d, 1H), 7.86 (s, 1H), 7.45-7.22 (m, 5H), 7.12 (d, 1H), 5.89 (s, 1H), 3.72-3.58 (m, 1H), 2.87 (t, 2H), 2.78-2.65 (m, 2H), 2.53 (t, 2H), 2.29 (s, 3H), 2.28-2.10 (m, 2H), 2.08-1.72 (m, 4H), 1.39 (s, 9H)

Example 210

2-[(1-methylpiperidin-4-yloxy)phenylmethyl]-3H-benzimidazol-4-ol

To a solution of (1-methylpiperidin-4-yloxy)phenylacetic acid (250mg) in acetonitrile (5mL) are added 2,3-diaminophenol (125mg), 2-chloro-1-methylpyridinium iodide (255mg) and dropwise diisopropylethylamine (0.44mL). The reaction mixture is stirred at room temperature for 3 hours. Solvent is removed under reduced pressure. Water is added to the residue and the solution is basified by adding a solution of saturated sodium carbonate to pH 10. The aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1).

The residue is dissolved in acetic acid (2mL) and the reaction mixture is refluxed for 24 hours. Acetic acid is removed under reduced pressure. Water is added to the residue and the solution is basified by adding a solution of saturated sodium carbonate to pH 10. The aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1). The residual solid is re-crystallized from hot toluene to give 2-[(1-methylpiperidin-4-yloxy)phenylmethyl]-3H-benzimidazol-4-ol melting at 170.5°C.

Example 211

[benzothiazol-2-yl(4'-methoxybiphenyl-3-yl)methyl](1-methylpiperidin-4-yl)amine, dioxalate

211A

[benzothiazol-2-yl(4'-methoxybiphenyl-3-yl)methyl](1-methylpiperidin-4-yl)amine, dioxalate melting at 130°C can be prepared according to general procedure 91A from benzothiazol-2-yl(4'-methoxybiphenyl-3-yl)methanol.

211B

A mixture of benzothiazol-2-yl(3-bromophenyl)methanol (200mg), 4-methoxyphenylboronic acid (142mg), tetrakis(triphenylphosphine)palladium (50mg), potassium carbonate (259mg), water (4mL), ethanol (1mL) and toluene (9mL) is purged with argon and refluxed for one night. After cooling at room temperature, the mixture is diluted with water and diethylether. The organic phase is dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by column chromatography (heptane / ethyl acetate 2 / 1) to afford benzothiazol-2-yl(4'-methoxybiphenyl-3-yl)methanol as a beige solid.

10

Example 217

3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}acrylonitrile

To a solution of 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzimidazole (230mg) in tetrahydrofuran (2.5mL) in a screw-capped tube are added acrylonitrile (0.15mL), triethylamine (2.5mL) and tetrakis(triphenylphosphine)palladium. The tube is evacuated, filled with argon, sealed and heated at 70 °C for 18h. Solvent and volatiles are removed under reduced pressure and the residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 95 / 5 / 0.5 to give 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}acrylonitrile.

¹H NMR: 7.98 (d, 1H), 7.88 (d, 1H), 7.65-7.55 (m, 2H), 7.55-7.35 (m, 5H), 5.92 (d, 1H), 5.88 (s, 1H), 4.00-3.90 (m, 1H), 3.25-2.95 (m, 4H), 2.65 (s, 3H), 2.50-2.35 (m, 2H), 2.25-2.00 (m, 2H)

Following compounds are prepared analogously:

Example	Product
205	3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}acrylic acid <i>tert</i> -butyl ester
	¹ H NMR: 7.98 (d, 1H), 7.87 (s, 1H), 7.68 (s, 1H), 7.60-7.36 (m, 6H), 6.37 (d, 1H), 5.93 (s, 1H), 3.72-3.59 (m, 1H), 2.80-2.65 (m, 2H), 2.29 (s, 3H), 2.28-2.10 (m, 2H), 2.05-1.60 (m, 4H), 1.74 (s, 9H).
209	2-[[3-(2-benzenesulfonylvinyl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
	¹ H NMR: 8.02-7.92 (m, 3H), 7.98 (d, 1H), 7.75-7.35 (m, 9H), 7.30-7.15 (m, 1H), 6.90 (d, 1H), 5.88 (s, 1H), 4.10-3.95 (m, 1H), 3.45-3.25 (m, 4H), 2.76 (s, 3H), 2.70-2.45 (m, 2H), 2.35-2.10 (m, 2H)

Example	Product
212	2-[[3-(2-methanesulfonylvinyl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
¹ H NMR: 7.99 (d, 1H), 7.88 (s, 1H), 7.78-7.59 (m, 3H), 7.55-7.38 (m, 4H), 6.92 (d, 1H), 5.94 (s, 1H), 3.78-3.62 (m, 1H), 3.03 (s, 3H), 2.87-2.70 (m, 2H), 2.32 (s, 3H), 2.40-2.13 (m, 2H), 2.10-1.75 (m, 4H)	

Example 219

3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]-*N*-benzyl-*N*-methylbenzamide

- 5 A screw-capped tube is charged with 2-[(3-bromo-phenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (example 27, 400 mg), *N*-benzylmethylamine (178 µL), 1,8-diazabicyclo(5.4.0)undec-7-ene (100 µL), trans-di- μ -acetatobis[2-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (22 mg), tri-*tert*-butylphosphonium tetrafluoroborate (17mg), molybdenum hexacarbonyl (127mg) and tetrahydrofuran (3mL). The tube is
- 10 sealed and heated at 125°C for 10min. The reaction was allowed to cool to room temperature and concentrated under reduced pressure. The residue is purified over silica gel (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.5 to 95 / 5 / 0.5) to afford 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]-*N*-benzyl-*N*-methylbenzamide which is then converted into its oxalate salt in acetone to give 3-[benzothiazol-
- 15 2-yl(1-methylpiperidin-4-yloxy)methyl]-*N*-benzyl-*N*-methylbenzamide, oxalate melting at 103°C.

Example 224

3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylamine

20 224A

- To a solution of 2-[(1-methylpiperidin-4-yloxy)(3-nitrophenyl)methyl]-1*H*-benzimidazole (110mg) in ethanol is added tin(II)dichloride (340mg). The reaction mixture is refluxed for 2 hours. The solution is basified by adding a solution of 10N sodium hydroxide to pH 10. The aqueous phase is extracted with chloroform. The pooled organic
- 25 extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1) to give 3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylamine melting at 100°C.

224 B

2-[(1-Methylpiperidin-4-yloxy)(3-nitrophenyl)methyl]-1*H*-benzimidazole can be prepared according to the method described in example 165.

5 Example 228

3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy-methyl}-phenylamine, oxalate

A suspension of 2-[(1-methylpiperidin-4-yloxy)[3-(3-nitro-benzyloxy)phenyl]-methyl]benzothiazole (example 196, 55mg) and tin(II) chloride dihydrate (250mg) in
10 ethanol (2mL) is refluxed for 1h. The cooled mixture is diluted with dichloromethane and aqueous 1N sodium hydroxide. The organic phase is dried over magnesium sulfate and concentrated under reduced pressure to afford 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy-methyl}-phenylamine which is then converted into its oxalate salt in acetone to give 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]
15 phenoxy-methyl}-phenylamine, oxalate as an orange solid. TLC of the base (eluent: CH₂Cl₂/MeOH/NH₄OH 95/5/0.5): R_f= 0.14.

Example 229

2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
20 enantiomer A

A solution of racemic 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol (10mg/mL) in a mixture of heptane / isopropanol (75 / 25) containing diethylamine (0.1%) is injected (20x100μL) onto an analytical Chiralcel OD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (80 /
25 20) containing diethylamine (0.1%) at a flow of 1mL/min. Products are detected at 220nm.

The first enantiomer has a retention time of 7.0min.

Collection affords 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol enantiomer A with a chromatographic enantiomeric purity of 100.0%.

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Example 230

2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
enantiomer B

The second enantiomer has a retention time of 9.4min.

Collection affords 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol enantiomer B with a chromatographic enantiomeric purity of 97.8%.

5 Example 231

2-[(3-azidophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
231A

To a solution of 3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-phenylamine (57mg) in methanol (3mL) are added at 0°C copper(II) sulphate and a
10 solution of trifluoromethanesulfonylazide (freshly prepared from sodium azide (220mg) and trifluoromethanesulfonic anhydride (200mg)) in dichloromethane.

The reaction mixture is stirred overnight at 4°C. Volatiles are removed under reduced pressure. Water is added to the residue and the solution is basified by adding a solution of saturated sodium carbonate to pH 10. The aqueous phase is extracted with
15 dichloromethane. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1) to give 2-[(3-azidophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole melting at 53°C.

20 231B

To a solution of 2-[(1-Methyl-piperidin-4-yloxy)-(3-nitro-phenyl)-methyl]-1*H*benzimidazole (110mg) in ethanol (5mL) is added Tin(II)dichloride-dihydrate (340mg). The reaction mixture is heated at reflux for 2 hours. Water is added to the mixture as well as sodium hydroxide 1N solution to pH 10. The solution is extracted with chloroform. The
25 pooled organic phases are dried with magnesium sulphate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1) to give 3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylamine that is used without further purification.

30 Example 234

{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}benzyl-amine,
dioxalate

A screw-capped tube is charged with 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (example 41, 190mg), copper(I) iodide (4mg), ethylene glycol
35 (45µL), potassium carbonate (173mg), benzylamine (54µL), and propan-2-ol (1mL). The tube is evacuated, filled with argon and sealed. After stirring at 80 °C for 15h, the mixture

is diluted with ethyl acetate and water and the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.5 to 95 / 5 / 0.5). The base is
5 converted into its dioxalate salt in acetone to give {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}benzyl-amine, dioxalate melting at 75°C.

Example 258

3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}propan-1-ol,
10 oxalate.

A screw-capped tube is charged with 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (example 41, 150mg), copper(I) iodide (6.5mg), 3,4,7,8-tetramethyl-1,10-phenanthroline (16.3mg), cesium carbonate (223mg), propan-1,3-diol (74mg), ground 4 Å molecular sieves (80mg) and toluene (4mL). The tube is evacuated,
15 filled with argon and sealed. After stirring at 90°C for 24h, the mixture is diluted with dichloromethane, water and ammonia. After filtration and decantation, the aqueous phase is extracted with dichloromethane. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.5 to 95 /
20 5 / 0.5). The base is converted into its oxalate salt in acetone to give 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}propan-1-ol, oxalate melting at 79°C.

Example 240

2-[(1-methylpiperidin-4-yloxy)[3-(2-[1,2,3]triazol-2-yl-ethylsulfanyl)phenyl]-
25 methyl]benzothiazole

240A

To a solution of 1,2,3-triazole (36.5mg) in *N,N*-dimethylformamide (1mL) is added a dispersion of sodium hydride 60% in mineral oil (1 molar equivalent). The reaction mixture is stirred at room temperature for 15 minutes, then a solution of methanesulfonic acid 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl ester
30 (85mg) in *N,N*-dimethylformamide (1mL) is added. The reaction mixture is stirred at 60°C overnight. Water is added and the aqueous phase is extracted by ethyl acetate. The organic phase is dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by column chromatography (gradient dichloromethane / methanol /
35 ammonia 100 / 0 / 0 to 90 / 10 / 1) to afford 2-[(1-methylpiperidin-4-yloxy)[3-(2-[1,2,3]triazol-2-yl-ethylsulfanyl)phenyl]methyl]benzothiazole.

¹H NMR: 7.97 (d, 1H), 7.87 (d, 1H), 7.65-7.25 (m, 8H), 5.90 (s, 1H), 4.62 (t, 2H), 3.75-3.60 (m, 1H), 3.44 (t, 2H), 2.82-2.65 (m, 2H), 2.29 (s, 3H), 2.45-2.15 (m, 2H), 2.10-1.70 (m, 4H)

and

5 2-[(1-methylpiperidin-4-yloxy)[3-(2-[1,2,3]triazol-1-yl-ethylsulfanyl)phenyl]methyl]-benzothiazole

¹H NMR: 7.95 (d, 1H), 7.87 (d, 1H), 7.86 (s, 1H), 7.61 (s, 1H), 7.56(s, 1H), 7.51-7.25 (m, 5H), 5.90 (s, 1H), 4.52 (t, 2H), 3.75-3.60 (m, 1H), 3.39 (t, 2H), 2.82-2.65 (m, 2H), 2.31 (s, 3H), 2.35-2.15 (m, 2H), 2.08-1.70 (m, 4H).

10

240B

Methanesulfonic acid 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl ester

To a solution of 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)-
15 methyl]phenylsulfanyl}ethanol (400mg) in dichloromethane (5mL) is added methanesulfonylchloride (1.25 molar equivalent) in dichloromethane (1.5mL) and triethylamine (1.5 molar equivalent). The reaction mixture is stirred overnight at room temperature. Volatiles are removed under reduced pressure to dryness. Water is added and the aqueous phase is extracted by diethylether. The organic phase is dried over
20 magnesium sulfate and concentrated. The residue is purified by column chromatography (dichloromethane / methanol from 98 / 2) to afford methanesulfonic acid 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl ester that will be used without further purification.

25

Example 245

2-[(1-methylpiperidin-4-yloxy)(3-vinyl-phenyl)methyl]-1*H*-benzimidazole

In a screw-cap tube are placed 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]benzimidazole (200mg), potassium vinyltrifluoroborate (72mg), 1,1-bis(diphenylphosphino)ferrocene-dichloro-palladium (7.5mg) and n-propanol (3mL). The
30 reaction mixture is degassed and purged with argon. The mixture is heated at reflux for 48h. Water and ammonia solution are added and the aqueous phase is extracted by ethyl acetate. The organic phase is dried over magnesium sulfate and concentrated. The residue is purified by column chromatography (gradient dichloromethane / methanol from 95 / 5 to 90 / 10 then dichloromethane / methanol / ammonia 90 / 10 / 0.1) to give 2-[(1-methylpiperidin-4-yloxy)(3-vinyl-phenyl)methyl]-1*H*-benzimidazole.
35

¹H NMR: 7.68-7.55 (m, 2H), 7.48 (s, 1H), 7.45-7.33 (m, 3H), 7.33-7.20 (m, 2H), 6.65 (dd, 1H), 5.83 (s, 1H), 5.75 (d, 1H), 5.26 (d, 1H), 3.88-3.75 (m, 1H), 3.28-3.10 (m, 2H), 3.05-2.75 (m, 2H), 2.63 (s, 3H), 2.30-1.95 (m, 4H)

5 Example 249

2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-ethylamine

249A

To a solution of *N*-*tert*-butoxycarbonyl-2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine in dichloromethane (2mL) is added trifluoroacetic acid (0.5ml) at room temperature. The mixture is stirred at room temperature for 24h. Water is added and the mixture is basified by adding a solution of sodium hydroxide. The aqueous phase is extracted by ethyl acetate. The organic phase is washed by water, then dried over magnesium sulfate and concentrated. The residue is triturated in diisopropylether to give 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine.

¹H NMR: 7.80-7.65 (m, 1H), 7.51 (s, 1H), 7.48-7.15 (m, 7H), 5.85 (s, 1H), 3.65-3.53 (m, 1H), 3.08-2.95 (m, 2H), 2.95-2.80 (m, 2H), 2.80-2.60 (m, 2H), 2.25 (s, 3H), 2.18-1.62 (m, 6H)

249B

N-*tert*-butoxycarbonyl-2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine could be prepared using method described in example 150A.

Example 252

2-[(1-methylpiperidin-4-yloxy)-*p*-tolylmethyl]-1*H*-benzimidazole enantiomer A

A solution of 2-[(1-methylpiperidin-4-yloxy)-*p*-tolylmethyl]-1*H*-benzimidazole (10mg/mL) in methanol containing diethylamine (0.1%) is injected (17x100μL) onto an analytical Ceraspher chiral RU-1, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (80 / 20) containing diethylamine (0.1%) at a flow of 1mL/min. Products are detected at 220nm.

The first enantiomer has a retention time of 10.4min.

Collection affords 2-[(1-methylpiperidin-4-yloxy)-*p*-tolylmethyl]-1*H*-benzimidazole enantiomer A with a chromatographic enantiomeric purity of 90%.

Example 253

2-[(1-methylpiperidin-4-yloxy)-p-tolylmethyl]-1*H*-benzimidazole enantiomer B

The second enantiomer has a retention time of 13.7min.

Collection affords 2-[(1-methylpiperidin-4-yloxy)-p-tolylmethyl]-1*H*-benzimidazole
5 enantiomer B with a chromatographic enantiomeric purity of 90%.

Example 259

2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-*N*-
methylacetamide

10 259A

To a solution of methylamine hydrochloride (76mg) in toluene (2mL) is added a 2N
solution of trimethylaluminum in toluene. The reaction mixture is heated at 60°C for 1
hour. Then a solution of {3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)-
methyl]phenylsulfanyl}acetic acid methyl ester (50mg) in toluene (1mL) is added. The
15 reaction mixture is heated at 60°C for 24 hours. Water is added to the reaction mixture,
pH is adjusted to 10 with a solution of sodium hydroxide, and the mixture is filtered on
celite. The filtrate is extracted with ethyl acetate. The pooled organic extracts are dried
over magnesium sulfate and concentrated under reduced pressure. The residue is purified
by chromatography (toluene / acetone / triethylamine 80 / 20 / 0.2) to give 2-{3-
20 [benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-*N*-methylacetamide.

¹H NMR (DMSO-d⁶): 8.12-7.97 (m, 2H), 7.89 (d, 1H), 7.52-7.22 (m, 6H), 5.90 (s,
1H), 3.60 (s, 2H), 3.59-3.45 (m, 1H), 2.62-2.40 (m, 5H), 2.03 (s, 3H), 2.03-1.82 (m, 4H),
1.82-1.45 (m, 4H)

25 259B

{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid
methyl ester can be obtained using method described in example 150.

Example 260

30 2-[(1-methylpiperidin-4-yloxy)[3-(2H-pyrazol-3-yl)phenyl]methyl]benzothiazole
260A

A solution of 2-((1-Methyl-piperidin-4-yloxy)-{3-[2-(2-trimethylsilanyl-ethoxymethyl)-
2H-pyrazol-3-yl]-phenyl}-methyl)-benzothiazole (500mg) in 5N hydrochloric acid (4mL) is
stirred overnight at room temperature. 30% sodium hydroxide solution is added to reach
35 pH 10, and the reaction is diluted with water. The aqueous phase is extracted with ethyl
acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated

under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol from 100 / 0 to 90 / 10) to afford 2-((1-methylpiperidin-4-yloxy)[3-(2H-pyrazol-3-yl)phenyl]methyl)benzothiazole melting at 90°C.

5 260B

2-((1-Methyl-piperidin-4-yloxy)-{3-[2-(2-trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-yl]-phenyl}-methyl)-benzothiazole can be prepared according to the method described in example 53.

10 Example 264

{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid hydrazide

To a solution of {3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid methyl ester (30mg) in absolute ethanol (1mL) is added
15 hydrazine hydrate (0.1mL). The reaction mixture is heated at 80 °C for 18 hours. Solvent and volatiles are removed under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol from 95 / 5 to 80 / 20) to give {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid hydrazide.

¹H NMR (DMSO-d⁶): 10.30 and 10.15 (two singlets, 1H), 8.05 (d, 1H), 7.89 (d, 1H),
20 7.50-7.20 (m, 6H), 5.99 (s, 1H), 3.89 (d, 2H), 3.58-3.45 (m, 1H), 2.75-2.50 (m, 2H), 2.09 (s, 3H), 2.08-1.95 (m, 2H), 1.90-1.50 (m, 6H)

Example 268

2-(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-
25 cyclopropyl)ethanol

268A

To a solution of 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}cyclopropanecarboxylic acid methyl ester (56mg) in tetrahydrofuran (5mL) is added lithium aluminumhydride (25mg) at 0 °C. The reaction mixture is allowed to
30 reach room temperature and ethyl acetate (2mL) is added. After stirring for 5 minutes, a half-saturated aqueous solution of sodium carbonate (6mL) is added. The aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 95 / 5
35 / 0.5) to afford 2-(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}cyclopropyl)ethanol.

¹H NMR: 7.97 (d, 1H), 7.87 (d, 1H), 7.56 (s, 1H), 7.52-7.22 (m, 5H), 5.86 (s, 1H), 3.72 (t, 2H), 3.72-3.58 (m, 1H), 2.98 (dd, 2H), 2.82-2.78 (m, 2H), 2.27 (s, 3H), 2.27-2.10 (m, 3H), 2.10-1.75 (m, 4H), 1.78 (t, 2H), 0.44 (m, 4H)

5 268B

1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-cyclopropanecarboxylic acid methyl ester can be obtained according to the method described in example 150.

10 Further examples can be prepared according to the above described general method:

Example	Product
257	2-(1-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-cyclopropyl)ethanol
¹ H NMR: 10.0 (sl, 1H), 7.60 (s, 1H), 7.80-7.35 (m, 2H), 7.32-7.15 (m, 5H), 5.82 (s, 1H), 3.75 (t, 2H), 3.68-3.50 (m, 1H), 3.01 (dd, 2H), 2.90-2.70 (m, 2H), 2.30 (s, 3H), 2.27-2.10 (m, 2H), 2.10-1.75 (m, 5H), 1.67 (t, 2H), 0.45 (m, 4H)	

Example 275

15 1-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyloxy)-propan-2-one, oxalate

A screw-capped tube is charged with 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (example 41, 300mg), copper(I) iodide (10mg), tetrakis palladium (36mg), triethylamine (0.33mL), 1-methyl-2-pyrrolidinone (1.3mL), and 1-prop-2-ynyloxypropan-2-one (109mg). The tube is evacuated, filled with argon and sealed. After stirring at 80°C for one night, the mixture is diluted with ethyl acetate and water and the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.5 to 95 / 5 / 0.5). The base is converted into its oxalate salt in acetone to give 1-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyloxy)-propan-2-one, oxalate. TLC of the base (eluent: CH₂Cl₂/MeOH/NH₄OH 95/5/0.5): R_f = 0.18.

Example 276

30 1-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyloxy)-propan-2-ol, oxalate

A solution of 1-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyloxy)-propan-2-one (example 275, 140mg) in methanol (20mL) is treated with sodium borohydride (30mg) at 0°C, stirred 1h at 0°C and 2h at room temperature. The mixture is then diluted with water and extracted with ethyl acetate. The pooled organic
 5 extracts are dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.5 to 95 / 5 / 0.5) affords the pure base that is then converted into its oxalate salt in acetone to give 1-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyloxy)-propan-2-ol, oxalate. TLC of the base (eluent:
 10 CH₂Cl₂/MeOH/NH₄OH 95/5/0.5): R_f= 0.12.

Example 278 *N*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine

278A

15 To a solution of 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)-methyl]phenylsulfanyl}ethylamine (130mg) in acetonitrile (2mL) is added *N,N'*-bis-Boc-guanylpurazole (112mg) and diisopropylethylamine (0.066mL) at room temperature. The mixture is heated at 50°C for 5h. Water is added and the aqueous phase is extracted by ethyl acetate. The organic phase is dried over magnesium sulfate and concentrated. The
 20 residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 95 / 5 / 0 to 90 / 10 / 0 then 90 / 10 / 1).

The residue is then dissolved in 6N aqueous hydrochloric acid (1.5mL) and the solution is stirred overnight at room temperature. The reaction mixture is neutralized to pH7 by adding dropwise 30% sodium hydroxide solution. The solvent is removed under
 25 reduced pressure and the residue is triturated with a (dichloromethane / methanol)(95 / 5) and filtered. The filtrate is evaporated under reduced pressure to give *N*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine as the dihydrochloride salt.

$$m/z : [M+H]^+ = 439.0$$

30

278B

2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-ethylamine can be prepared as described in example 249.

Following compounds are prepared analogously:

Example	Product
394	4-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-

Example	Product
	yloxy)methyl]phenyl]piperidine-1-carboxamide hydrochloride
¹ H NMR (DMSO-d ⁶): 7.48-7.38 (m, 2H), 7.34 (s, 1H), 7.32-7.20 (m, 2H), 7.17-7.00 (m, 3H), 5.78 (s, 1H), 3.98 (sl, 1H), 3.92 (sl, 1H), 2.88-2.50 (m, 4H), 2.07 (s, 3H), 2.00-1.75 (m, 4H), 1.75-1.45 (m, 6H)	

Example 293

4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}butylamine, dichlorhydrate

5 293A

To a solution of 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)-methyl]phenyl}but-3-ynylamine (50mg) in methanol (2.5mL) is added platinum oxide (8mg). The flask is purged with argon then put under one atmosphere of hydrogen. The reaction mixture is stirred overnight at room temperature then filtered on celite, cake
10 washed with methanol. The solvent is removed under reduced pressure to give 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}butylamine.

m/z : $[M+H]^+ = 393.1$; $[M+Na]^+ = 415.2$

293B

15 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynylamine can be prepared according to general method in example 194.

Following compounds are prepared analogously:

Example	Product
238	4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}butan-1-ol
¹ H NMR: 7.98 (d, 2H), 7.87 (d, 1H), 7.50-7.25 (m, 6H), 7.13 (d, 1H), 5.88 (s, 1H), 3.81-3.70 (m, 1H), 7.70-7.60 (m, 2H), 3.98-2.80 (m, 2H), 2.65 (t, 2H), 2.43 (s, 3H), 2.22-1.50 (m, 10H), 1.34 (t, 1H)	
396	2-[(1-methylpiperidin-4-yloxy)[3-(2-piperidin-4-yl-ethyl)phenyl]methyl]-1 <i>H</i> -benzimidazole
¹ H NMR: 7.65-7.50 (m, 2H), 7.35-7.15 (m, 5H), 7.03 (d, 1H), 5.85 (s, 1H), 3.75 (t, 2H), 3.65-3.50 (m, 1H), 3.45-3.30 (m, 2H), 2.90-2.65 (m, 4H), 2.58-2.45 (m, 2H), 2.28 (s, 3H), 2.28-2.10 (m, 2H), 2.10-1.65 (m, 5H), 1.65-1.35 (m, 4H)	

20

Following compounds are prepared according to the general methods:

Example	Product	General methods	m/z
98	{3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-yl}acetonitrile, oxalate	53	[M+H] ⁺ = 454.2
139	2-[(3'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole	53	[M+H] ⁺ = 433.1
140	2-[(1-methylpiperidin-4-yloxy)(4'-trifluoromethylbiphenyl-3-yl)methyl]benzothiazole	53	[M+H] ⁺ = 483.2
141	2-[(1-methylpiperidin-4-yloxy)(2',3',4'-trifluorobiphenyl-3-yl)methyl]benzothiazole	53	[M+H] ⁺ = 468.6
143	{3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)-methyl]biphenyl-4-yl}carbamic acid <i>tert</i> -butyl ester	53	[M+H] ⁺ = 530.2
320	<i>N</i> -(3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propyl)guanidine, trihydrochloride	278A, 249, 149A	[M+H] ⁺ = 421.0
321	<i>N</i> -(3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propyl)guanidine, trihydrochloride	278A, 249, 149A	[M+H] ⁺ = 421.2 [M+Na] ⁺ = 443.2
344	6-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hexylamine	293, 194	[M+H] ⁺ = 421.2
346	<i>N</i> -(6-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine, hydrochloride	278A, 249, 149A	[M+H] ⁺ = 459.2
355	<i>N</i> -(6-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hexyl)guanidine, trihydrochloride	278A, 249, 149A	[M+H] ⁺ = 463.2 [M+Na] ⁺ = 485.3
358	<i>N</i> -(5-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)guanidine, hydrochloride	278A, 249, 149A	[M+H] ⁺ = 445.2 [M+Na] ⁺ = 467.3
372	<i>N</i> -(4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine, dihydrochloride	278A, 249, 149A	[M+H] ⁺ = 448.1
393	<i>N</i> -(4-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-	278A,	[M+H] ⁺ =

Example	Product	General methods	m/z
	yloxy)methyl]phenyl}but-3-ynyl)guanidine, hydrochloride	249, 149A	431.1
397	<i>N</i> -(5-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pentyl)guanidine, hydrochloride	278A, 249, 149A	[M+H] ⁺ = 449.2 [M+Na] ⁺ = 471.2
418	<i>N</i> -(3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)guanidine, hydrochloride	278A, 249, 149A	[M+H] ⁺ = 417.1
426	3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylethynyl}azetidine-1-carboxamidine	278A, 249, 149A	[M+H] ⁺ = 443.1 [M+Na] ⁺ = 465.4

Example 298

(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-ethyl)urea

5 298A

To a solution of 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)-methyl]phenylsulfanyl}ethylamine

(50mg) in ethanol (0.5mL) in a screw-cap tube is added potassium cyanate (15mg). The reaction mixture is heated at 80°C for 24 hours. The mixture is diluted water, basified to pH 9 by adding of an aqueous saturated solution of sodium carbonate and extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 95 / 5 / 0.5 to 90 / 10 / 1) to afford (2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)urea melting at 136°C.

298B

2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-ethylamine can be prepared according to the method described in example 249.

20

Following compounds are prepared analogously:

Example	Product
299	(2-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)(4,5-dihydrothiazol-2-yl)amine
	¹ H NMR (DMSO-d ⁶): 12.37 (sl, 1H), 7.53-7.38 (m, 3H), 7.27-6.95 (m, 5H), 5.80 (s, 1H), 3.80 (t, 2H), 3.45-3.00 (m, 7H), 2.65-2.50 (m, 2H), 2.07 (s, 3H), 2.00-1.75 (m, 4H), 1.65-1.45 (m, 2H)
317	(2-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)(4,5-dihydro-1 <i>H</i> -imidazol-2-yl)amine
	¹ H NMR (DMSO-d ⁶): 12.90 (sl, 1H), 10.80 and 10.40 (sl, 1H), 8.58-8.42 (m, 1H), 7.53-7.38 (m, 3H), 7.27-6.95 (m, 5H), 5.93 (s, 1H), 3.80 (t, 2H), 3.45-3.00 (m, 7H), 2.65-2.50 (m, 2H), 2.07 (s, 3H), 2.00-1.75 (m, 4H), 1.65-1.45 (m, 2H)
347	1-(2-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-3-isopropylthiourea
	¹ H NMR: 10.43 (sl, 1H), 7.72-7.50 (m, 3H), 7.35-7.20 (m, 5H), 6.45-6.15 (m, 2H), 5.83 (s, 1H), 4.05-3.50 (m, 4H), 3.45-3.05 (m, 2H), 3.00-2.75 (m, 2H), 2.39 (s, 3H), 2.20-1.75 (m, 4H), 1.22 (m, 1H), 1.02 (d, 3H), 0.91 (d, 3H)

Example 305

5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-pentylamine, oxalate

5 305A

2-(5-{3-[(1*H*-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-pentyl)isoindole-1,3-dione (200mg) is dissolved in ethanol (1mL) and hydrazine hydrate (0.1mL) is added. The reaction mixture is stirred at room temperature overnight. The mixture is evaporated to dryness and the residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1). The residue is added to oxalic acid (1 equivalent) in acetone (0.5ml), and the precipitate is filtered and dry to give 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-pentylamine, oxalate melting at 201 °C.

15 305B

2-(5-{3-[(1*H*-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-pentyl)isoindole-1,3-dione

A screw-cap tube is charged with 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (200mg), palladium bis(dibenzylideneacetone) (14mg), Xantphos (14mg), thioacetic acid 5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentyl ester

(209mg), diisopropylethylamine (170 μ L), potassium phosphate (105mg), water (0.05mL) and 1,4-dioxane (2mL). The tube is evacuated, filled with argon and sealed. After stirring at 120 °C for 48h, solvents are removed under reduced pressure. The residual solution is basified by adding a solution of saturated sodium carbonate to pH 10 and the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 95 / 5 / 0.5) to give 2-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylpentyl}isoindole-1,3-dione that is used without further purification.

Example 307

N-*tert*-butoxycarbonyl-*N'*-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine

307A

To a solution of 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)-methyl]phenyl}but-3-ynylamine (290mg) in acetonitrile (4.5mL) is added *N,N'*-bis-Boc-guanylpurazole (255mg) and diisopropylethylamine (0.15mL) at room temperature. The mixture is heated at 50 °C overnight. Water is added and the aqueous phase is extracted by ethyl acetate. The organic phase is dried over magnesium sulfate and concentrated. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 95 / 5 / 0 to 90 / 10 / 0 then 90 / 10 / 1).

A part of the residue (100mg) is then dissolved in 1,2-dichloroethane (2mL) ; phenol (149mg) and chlorotrimethylsilane (0.2mL) are added and the solution is heated at 50 °C for 20h. Solvent and volatiles are removed under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 95 / 5 / 0 to 90 / 10 / 0 then 90 / 10 / 1) to give *N*-*tert*-butoxycarbonyl-*N'*-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine.

¹H NMR: 7.54 (sl, 2H), 7.32 (s, 1H), 7.27-7.19 (m, 6H), 5.67 (s, 1H), 3.70-3.52 (m, 1H), 3.52-3.32 (m, 2H), 2.85-2.65 (m, 2H), 2.61 (t, 2H), 2.24 (s, 3H), 2.20-2.02 (m, 2H), 1.92-1.50 (m, 4H), 1.49 (t, 9H)

307B

4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynylamine can be prepared as described in example 194A.

Example 315

2-((1-methylpiperidin-4-yloxy)[3-(4-[1,2,3]triazol-2-yl-butoxy)phenyl]methyl)-
benzothiazole, oxalate

315A

60% in oil sodium hydride (20mg) is washed with pentane and diluted with
5 anhydrous *N,N*-dimethylformamide (5mL). 1*H*-1,2,3-triazole is then added. After stirring at
room temperature for 15 min, the mixture is treated with 2-[[3-(4-chloro-butoxy)phenyl]-(1-
methyl-piperidin-4-yloxy)methyl]benzothiazole (223mg) and warmed at 60 °C for one night.
The mixture is then poured into water and extracted with diethylether. The pooled organic
extracts are dried over magnesium sulfate and concentrated under reduced pressure.
10 Purification of the residue by chromatography (gradient dichloromethane / methanol /
ammonia from 98 / 2 / 0.5 to 90 / 10 / 0.5) affords the pure base that is then converted into
its oxalate salt in acetone to give 2-((1-methylpiperidin-4-yloxy)[3-(4-[1,2,3]triazol-2-yl-
butoxy)phenyl]methyl)benzothiazole, oxalate. TLC of the base (eluent:
CH₂Cl₂/MeOH/NH₄OH 90/10/0.5): R_f= 0.30.

15

315B

2-[[3-(4-Chlorobutoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole can
be prepared according to the described general methods 272A and 1B.

20

Example 316

2-((1-methylpiperidin-4-yloxy)[3-(4-[1,2,4]triazol-1-yl-butoxy)phenyl]methyl)-
benzothiazole, oxalate

2-((1-methylpiperidin-4-yloxy)[3-(4-[1,2,4]triazol-1-yl-butoxy)phenyl]methyl)-
benzothiazole, oxalate can be prepared according general procedure 315A. TLC of the
25 base (eluent: CH₂Cl₂/MeOH/NH₄OH 90/10/0.5): R_f= 0.22.

Example 318

N-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-
ethyl)-*N'*-cyanoguanidine

30

318A

To a solution of 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)-
methyl]phenylsulfanyl}ethylamine (50mg) in isopropanol (1mL) in a screw-cap tube is
added diphenylcyanocarbonimidate (30mg). The reaction mixture is stirred at room
temperature overnight. Solvent is removed under reduced pressure and the residual solid
35 is dried. This solid is dissolved in ethanol (2mL) saturated with ammonia gas in a screw-
cap tube. The tube is sealed and the reaction mixture is heated to 80 °C for 2 hours. The

solvent and volatiles are removed under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1) to afford *N*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-*N'*-cyanoguanidine melting at 65 °C.

5

318B

2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-ethylamine can be prepared according to the method described in example 249.

10

Example 338

2-[(1-methylpiperidin-4-yloxy)[3-(1,2,3,6-tetrahydro-pyridin-4-yl)phenyl]methyl]-1*H*-benzimidazole

338A

To a solution of 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)-methyl]phenyl}-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (407mg) in dichloromethane (2mL) is added trifluoroacetic acid (1mL). After 2 hours at room temperature, volatiles are removed under reduced pressure. The mixture is diluted with water, basified to pH 10 by adding of an aqueous saturated solution of sodium carbonate and extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 85 / 15 / 1.5) to afford 2-[(1-methylpiperidin-4-yloxy)[3-(1,2,3,6-tetrahydro-pyridin-4-yl)phenyl]methyl]-1*H*-benzimidazole.

¹H NMR: 10.0 (sl, 1H), 7.60 (s, 1H), 7.70-7.45 (m, 2H), 7.40-7.20 (m, 5H), 6.06 (s, 1H), 5.87 (s, 1H), 3.50 (t, 2H), 3.65-3.45 (m, 1H), 3.08 (d, 2H), 2.80-2.75 (m, 2H), 2.60-2.22 (m, 3H), 2.26 (s, 3H), 2.20-1.65 (m, 6H)

338A

4-{3-[(1*H*-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester can be prepared according to the procedure described in example 53.

Example 359

4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-butylamine, oxalate

359A

35

(4-{3-[Benzothiazol-2-yl-(1-methyl-piperidin-4-yloxy)-methyl]-phenylsulfanyl}-butyl)-carbamic acid *tert*-butyl ester (140mg) is dissolved in dichloromethane (1mL) and trifluoroacetic acid (0.4mL) is added. The reaction mixture is stirred at room temperature for 1 hour. The mixture is evaporated to dryness. The residue is basified by adding a solution of saturated sodium carbonate to pH 10 and the aqueous phase is extracted with dichloromethane. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 90 / 10 / 1). The residue is added to oxalic acid (1 equivalent) in acetone (0.5ml), and the precipitate is filtered and dry to give 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)-methyl]phenylsulfanyl}butylamine, oxalate melting at 108°C.

359B

(4-{3-[(1*H*-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-butyl)carbamic acid *tert*-butyl ester.

A screw-cap tube is charged with 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (200mg), palladium bis(dibenzylideneacetone) (14mg), Xantphos (14mg), thioacetic acid S-(4-*tert*-butoxycarbonylaminobutyl) ester (180mg), potassium phosphate (200mg), water (0.01mL) and 1,4-dioxane (2mL). The tube is evacuated, filled with argon and sealed. After stirring at 120°C for 48h, solvents are removed under reduced pressure. The residue is basified by adding a solution of saturated sodium carbonate to pH 10 and the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 95 / 5 / 0.5) to give (4-{3-[(1*H*-benzimidazol-2-yl)-(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butyl)carbamic acid *tert*-butyl ester that is used without further purification.

Example 376

2-[(1-methylpiperidin-4-yloxy)(3-piperidin-4-ylethynyl-phenyl)methyl]-1*H*-benzimidazole

376A

To a solution of 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)-methyl]phenylethynyl}piperidine-1-carboxylic acid *tert*-butyl ester (160mg) in 1,2-dichloroethane (10mL) are added phenol (940mg) and chlorotrimethylsilane (1.26mL). The reaction mixture is heated to 100°C for 30 minutes. Volatiles are removed under reduced

pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 85 / 15 / 1.5) to afford 2-[(1-methylpiperidin-4-yloxy)(3-piperidin-4-ylethynyl-phenyl)methyl]-1*H*-benzimidazole.

¹H NMR: 9.80 (sl, 1H), 7.50 (s, 1H), 7.80-7.50 (m, 2H), 7.45-7.20 (m, 5H), , 5.84 (s, 1H), 3.65-3.50 (m, 1H), 3.25-3.10 (m, 2H), 2.90-2.35 (m, 7H), 2.25 (s, 3H), 2.20-1.65 (m, 9H)

376B

4-{3-[(1*H*-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylethynyl}-piperidine-1-carboxylic acid *tert*-butyl ester can be prepared according to the procedure described in example 189.

Example 384

5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-en-1-ol
384A

To a solution of Acetic acid 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-enyl ester (150mg) in a mixture of water (1mL), 1,4-dioxane (1mL) and methanol (1mL) is added 1N sodium hydroxide solution (0.6mL). The reaction mixture is stirred at room temperature for 2 hours. After neutralization to pH 7 with addition of 1N hydrochloric acid, the reaction mixture is extracted with dichloromethane. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 95 / 5 / 0.5 to 90 / 10 / 1) to afford 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-en-1-ol.

¹H NMR: 7.97 (d, 1H), 7.86 (dd, 1H), 7.53-7.24 (m, 6H), 6.32 (dd, 1H), 6.27 (dd, 1H) 5.30 (s, 1H), 3.71 (t, 2H), 3.77-3.60 (m, 1H), 3.00-2.90 (m, 2H), 2.80-2.68 (m, 2H), 2.30 (s, 3H), 2.37-2.15 (m, 4H), 2.20-1.55 (m, 5H)

384B

Acetic acid 5-{3-[benzothiazol-2-yl-(1-methyl-piperidin-4-yloxy)-methyl]-phenyl}-pent-4-enyl ester can be prepared according to the method described in example 53.

Following examples can be prepared analogously:

Example	Product	General methods
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Example	Product	General methods
156	2-[[3-(2,5-difluorobenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	1A, 168B
¹ H NMR of the base (CDCl ₃): 7.96 (d, 1H), 7.85 (d, 1H), 6.90-7.50 (m, 9H), 5.86 (s, 1H), 5.10 (s, 2H), 3.83 (m, 1H), 2.97 (m, 2H), 2.83 (m, 2H), 2.61 (s, 3H), 2.20 (m, 2H), 1.93 (m, 2H).		
263	2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetamide	259A, 150
¹ H NMR (DMSO-d ₆): 8.03 (s, 1H), 7.86 (d, 1H), 7.61 (sl, 1H), 7.48-7.18 (m, 6H), 7.11 (sl, 1H), 5.95 (s, 1H), 3.57 (s, 2H), 3.57-3.45 (m, 1H), 2.62-2.40 (m, 2H), 2.07 (s, 3H), 2.07-1.72 (m, 4H), 1.70-1.35 (m, 2H)		
309	<i>N-tert</i> -butoxycarbonyl- <i>N'</i> -(4-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}butyl)guanidine	307A, 194A
¹ H NMR: 7.65-7.55 (m, 2H), 7.38 (s, 1H), 7.30-7.15 (m, 4H), 7.01 (d, 1H), 5.79 (s, 1H), 3.70-3.55 (m, 1H), 3.18-2.95 (m, 4H), 2.55-2.30 (m, 4H), 2.44 (s, 3H), 2.15-1.95 (m, 2H), 1.95-1.70 (m, 2H), 1.65-1.50 (m, 4H), 1.49 (s, 9H)		
313	<i>N-tert</i> -butoxycarbonyl- <i>N'</i> -(3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propyl)amine	307A, 194A
¹ H NMR: 7.68-7.58 (m, 2H), 7.52 (s, 1H), 7.30-7.15 (m, 4H), 7.01 (d, 1H), 5.79 (s, 1H), 3.85-3.70 (m, 1H), 3.45-3.18 (m, 4H), 2.78-2.50 (m, 4H), 2.62 (s, 3H), 2.20-1.60 (m, 6H), 1.46 (s, 9H)		
335	<i>N-tert</i> -butoxycarbonyl- <i>N'</i> -(3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pentyl)guanidine, hydrochloride	307A, 194A
¹ H NMR: 8.95 (sl, 1H), 7.68-7.58 (m, 2H), 7.41 (s, 1H), 7.32-7.15 (m, 4H), 7.01 (d, 1H), 5.78 (s, 1H), 3.92-3.82 (m, 1H), 3.70-3.25 (m, 4H), 3.20-2.70 (m, 4H), 2.81 (s, 3H), 2.52 (t, 2H), 2.30-1.85 (m, 4H), 1.70-1.50 (m, 2H), 1.49 (s, 9H), 1.35-1.20 (m, 2H)		
336	<i>N-tert</i> -butoxycarbonyl- <i>N'</i> -(3-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)guanidine	307A, 194A
¹ H NMR: 7.68-7.58 (m, 2H), 7.41 (s, 1H), 7.32-7.15 (m, 4H), 7.01 (d, 1H), 5.78 (s, 1H), 4.27 (s, 2H), 3.92-3.82 (m, 1H), 3.10-2.80 (m, 2H), 2.37 (s, 3H), 2.65-2.30 (m, 2H), 2.15-1.90 (m, 2H), 1.90-1.65 (m, 2H), 1.46 (s, 9H)		
345	<i>N-tert</i> -butoxycarbonyl- <i>N'</i> -(6-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine	307A, 194A

Example	Product	General methods
	¹ H NMR (DMSO-d ⁶): 10.91 (sl, 1H), 8.71 (sl, 1H), 7.65-7.48 (m, 2H), 7.48-7.15 (m, 6H), 6.00(s, 1H), 3.80 (s, 1H), 3.00-2.82 (m, 2H), 2.75 (m, 2H), 3.63 (m, 2H), 2.43 (s, 3H), 2.15-2.05 (m, 2H), 1.98-1.75 (m, 2H), 1.75-1.55 (m, 6H), 1.44 (s, 9H)	
351	4-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}propyl)piperazine-1-carboxylic acid <i>tert</i> -butyl ester, oxalate	370A, 272A and 1B
	¹ H NMR of the base (CDCl ₃): 7.96 (d, 1H), 7.82 (d, 1H), 7.50-7.20 (m, 3H), 7.07 (m, 2H), 6.79 (d, 1H), 5.86 (s, 1H), 3.97 (t, 2H), 3.60 (m, 1H), 3.40 (m, 4H), 2.67 (m, 2H), 2.48 (t, 2H), 2.36 (m, 4H), 2.23 (s, 3H), 2.13 (m, 2H), 2.00-1.70 (m, 6H), 1.44 (s, 9H)	
353	4-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}-3,6-dihydro-2H-pyridine-1-carboxamide, hydrochloride	376A, 189
	¹ H NMR (DMSO-d ⁶): 10.7 and 10.45 (sl, 1H), 7.68-7.50 (m, 1H), 7.50-7.35 (m, 2H), 7.28-7.10 (m, 5H), 6.20 (s, 1H), 5.95 (d, 1H), 4.06 (s, 2H), 3.79 (s, 1H), 3.58 (t, 2H), 3.05-2.80 (m, 2H), 2.74 (s, 2H), 2.65-2.50 (m, 2H), 2.48 (s, 3H), 2.25-2.05 (m, 2H), 2.00-1.75 (m, 2H)	
357	<i>N</i> - <i>tert</i> -butoxycarbonyl- <i>N'</i> -(5-{3-[(1 <i>H</i> -benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)guanidine	307A, 194A
	¹ H NMR (DMSO-d ⁶): 12.55 (sl, 1H), 8.67 (sl, 1H), 7.68-7.40 (m, 2H), 7.40-7.25 (m, 3H), 7.20-7.05 (m, 3H), 5.86(s, 1H), 3.78-3.50 (m, 1H), 3.10-2.80 (m, 2H), 2.75-2.50 (m, 4H), 2.46 (s, 3H), 2.20-1.65 (m, 8H), 1.42 (s, 9H)	
383	2-[(1-methylpiperidin-4-yloxy)[3-(pyrrolidin-3-yloxy)phenyl]methyl]benzothiazole, dioxalate	258
	¹ H NMR of the base (CDCl ₃): 7.98 (d, 1H), 7.87 (d, 1H), 7.46-7.20 (m, 3H), 7.09 (m, 2H), 6.80 (d, 1H), 5.89 (s, 1H), 4.83 (m, 1H), 3.63 (m, 2H), 3.17 (m, 1H), 3.00-2.85 (m, 2H), 2.68 (m, 2H), 2.28 (s, 3H), 2.20-1.70 (m, 8H)	
390	5-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-en-1-ol	384A, 53
	¹ H NMR: 7.97 (d, 1H), 7.86 (dd, 1H), 7.54 (s, 1H), 7.50-7.25 (m, 4H), 7.19 (d, 1H), 6.43 (dd, 1H), 6.27 (dd, 1H) 5.94 (s, 1H), 5.73 (dd, 1H), 3.77-3.60 (m, 3H), 2.87-2.70 (m, 2H), 2.55-2.20 (m, 2H), 2.33 (s, 3H), 2.20-1.65 (m, 7H)	

Example 385

3-amino-4-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamino)-cyclobut-3-ene-1,2-dione 385A

To a solution of 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)-methyl]phenylsulfanyl}ethylamine (150mg) in diethylether (10mL) is added L). The reaction mixture is stirred at □3,4-diethoxy-3-cyclobutene-1,2-dione (56 room temperature for 1 hour. The mixture is filtered, washed with diethylether and dried. The residue is dissolved in ethanol (2mL) saturated with ammonia gas in a screw-capped tube. The tube is sealed and the reaction mixture is heated to 80°C for 2 hours. The solvent and volatiles are removed under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1) to afford 3-amino-4-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamino) -cyclobut-3-ene-1,2-dione melting at 161 °C.

15 385B

2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-ethylamine can be prepared according to the method described in example 249.

Example 386

20 [[3-(6-aminohex-1-ynyl)phenyl](1*H*-benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine

386A

A solution of 2-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-ylamino)-methyl]phenyl}pent-4-ynyl)isoindole-1,3-dione (230mg) and hydrazine hydrate (120μL) in ethanol (3mL) is stirred a room temperature for one night. The mixture is then concentrated under reduced pressure and the residue purified by chromatography (dichloromethane / methanol / ammonia from 90 / 10 / 0.5) to afford [[3-(6-aminohex-1-ynyl)phenyl](1*H*-benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine melting at 79 °C.

30 386B

2-(5-{3-[(1*H*-Benzimidazol-2-yl)(1-methylpiperidin-4-ylamino)methyl]phenyl}pent-4-ynyl)isoindole-1,3-dione can be prepared according to general procedure 275 starting from [(1*H*-benzimidazol-2-yl)(3-iodo-phenyl)methyl](1-methylpiperidin-4-yl)amine.

Example 398

2-[[3-[3-(3*H*-imidazol-4-yl)propylsulfanyl]phenyl](1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

398A

5 To a solution of 2-((1-methylpiperidin-4-yloxy){3-[3-(1-trityl-1*H*-imidazol-4-yl)propylsulfanyl]phenyl}methyl)-1*H*-benzimidazole (200mg) in 1,2-dichloroethane (7mL) are added phenol (270mg) and chlorotrimethylsilane (0.37mL). The reaction mixture is heated at reflux overnight. Volatiles are removed under reduced pressure and the residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 /
10 2 / 0.2 to 90 / 10 / 1) to give 2-[[3-[3-(3*H*-imidazol-4-yl)propylsulfanyl]phenyl](1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole.

¹H NMR: 7.72-7.40 (m, 4H), 7.25-7.15 (m, 5H), 6.82 (s, 1H), 5.84 (s, 1H), 3.60-3.45 (m, 1H), 3.00-2.65 (m, 6H), 2.25 (s, 3H), 2.15-1.60 (m, 8H)

15 398B

2-((1-Methylpiperidin-4-yloxy){3-[3-(1-trityl-1*H*-imidazol-4-yl)propylsulfanyl]phenyl}methyl)-1*H*-benzimidazole can be prepared according to the method described in example 359A.

20 Example 401

N-acetyl-*N'*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine

401A

To a solution of *N*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine.dihydrochloride (100mg) in dry acetonitrile (1mL) is
25 added acetic anhydride (64mg) et 4-dimethylaminopyridine (51mg). After 24 hours at room temperature, solvent and volatiles are removed under reduced pressure. The residue is purified by chromatography (toluene / acetone / triethylamine 50 / 50 / 1 then gradient dichloromethane / methanol / ammonia from 95 / 5 / 0.5 to 90 / 10 / 1) to give *N*-
30 acetyl-*N'*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine.

¹H NMR (DMSO-*d*⁶): 12.40 (sl, 1H), 7.55-7.40 (m, 1H), 7.40-7.20 (m, 3H), 7.20-7.05 (m, 4H), 5.81 (s, 1H), 3.50-3.05 (m, 3H), 2.65-2.55 (m, 2H), 2.46 (s, 3H), 2.07 (s, 3H), 2.02-1.72 (m, 4H), 1.68-1.45 (m, 4H).

401B

N-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-ethyl)guanidine can be obtained according to the method described in example 278.

5 Example 403

1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}azetidin-3-ol, oxalate

A screw-capped tube is charged with 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (example 41, 150mg), copper(I) iodide (15mg), deanol (1mL),
10 potassium carbonate (306mg), azetidin-3-ol, hydrochloride (88mg). The tube is evacuated, filled with argon and sealed. After stirring at 60°C for 100h, the mixture is diluted with dichloromethane, water and ammonia. After decantation, the aqueous phase is extracted with dichloromethane. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by
15 chromatography (gradient dichloromethane / methanol / ammonia from 95 / 5 / 0.5 to 90 / 10 / 0.5). The base is converted into its oxalate salt in acetone to give 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}azetidin-3-ol, oxalate melting at 117°C.

20 Example 411

1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-ol, oxalate

A solution of acetic acid 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-yl ester (example 413, 100mg) and aqueous 1N sodium hydroxide in methanol (1mL) is stirred at room temperature for 30min. The mixture is
25 diluted water and extracted with dichloromethane. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 95 / 5 / 0.5 to 90 / 10 / 0.5). The base is converted into its oxalate salt in acetone to give 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-ol, oxalate melting
30 at 110°C.

Example 412

2-[(3-[2-(1*H*-imidazol-4-yl)ethyl]phenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

412A

To a solution of 2-[(1-methylpiperidin-4-yloxy)[3-(1-trityl-1*H*-imidazol-4-ylethynyl)phenyl]methyl]-1*H*-benzimidazole (260mg) in 1,2-dichloroethane (7mL) are added phenol (374mg) and chlorotrimethylsilane (0.51mL). The reaction mixture is heated at reflux overnight. Volatiles are removed under reduced pressure and the residue is purified by chromatography (gradient dichloromethane / methanol from 95 / 5 to 90 / 10 then dichloromethane / methanol / ammonia 90 / 10 / 1).

The residue is then dissolved in methanol (3mL) and palladium on charcoal (8mg) is added. The flask is purged with argon then put under one atmosphere of hydrogen. The reaction mixture is stirred overnight at room temperature then filtered on celite, cake washed with methanol. The solvent is removed under reduced pressure to give 2-[(3-[2-(1*H*-imidazol-4-yl)ethyl]phenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole.

¹H NMR(methanol-d⁴): 7.65-7.55 (m, 3H), 7.40-7.15 (m, 6H), 6.70 (s, 1H), 5.85 (s, 1H), 3.80-3.70 (m, 1H), 3.28-3.10 (m, 2H), 3.05-2.75 (m, 6H), 2.64 (s, 3H), 2.15-1.85 (m, 4H).

412B

2-[(1-Methylpiperidin-4-yloxy)[3-(1-trityl-1*H*-imidazol-4-ylethynyl)phenyl]methyl]-1*H*-benzimidazole can be prepared according to the method described in example 189.

Example 416

2-[(1-methylpiperidin-4-yloxy)[3-(5-[1,2,3]triazol-2-yl-pent-1-ynyl)phenyl]methyl]-1*H*-benzimidazole

416A

To a solution of 1,2,3-triazole (66mg) in DMF (0.6mL) is added sodium hydride (25mg). After gas evolution ceased, 2-[[3-(5-chloropent-1-ynyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole (50mg) and a catalytic quantity of *n*-tetrabutylammonium iodide are added. After stirring overnight at room temperature, the solvent is removed under reduced pressure to dryness. The residue is purified by chromatography (dichloromethane / methanol / ammonia 90 / 10 / 1) to afford 2-[(1-methylpiperidin-4-yloxy)[3-(5-[1,2,3]triazol-2-yl-pent-1-ynyl)phenyl]methyl]-1*H*-benzimidazole.

¹H NMR: 9.43 (sl, 1H), 7.83-7.68 (m, 1H), 7.60 (s, 2H), 7.52 (s, 1H), 7.50-7.20 (m, 6H), 5.84 (s, 1H), 4.61 (t, 2H), 3.68-3.50 (m, 1H), 2.88-2.70 (m, 2H), 2.46 (t, 2H), 2.30 (s, 3H), 2.38-2.10 (m, 4H), 2.10-1.65 (m, 6H).

416B

2-[[3-(5-Chloropent-1-ynyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole can be obtained according to the synthetic method described in example 189.

5

Following compounds are prepared analogously:

Example	Product
417	2-{{(1-methylpiperidin-4-yloxy)[3-(5-[1,2,3]triazol-1-ylpent-1-ynyl)phenyl]methyl}-1 <i>H</i> -benzimidazole
	¹ H NMR: 9.77 (sl, 1H), 7.83-7.68 (m, 1H), 7.70 (s, 1H), 7.61 (s, 1H), 7.52 (s, 1H), 7.50-7.35 (m, 2H) 7.35-7.20 (m, 4H), 5.84 (s, 1H), 4.58 (t, 2H), 3.70-3.55 (m, 1H), 2.90-2.75 (m, 2H), 2.47 (t, 2H), 2.32 (s, 3H), 2.40-2.15 (m, 4H), 2.15-1.70 (m, 4H)
409	2-[[3-(5-imidazol-1-ylpent-1-ynyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1 <i>H</i> -benzimidazole
	¹ H NMR: 10.90 (sl, 1H), 7.85-7.68 (m, 1H), 7.69 (s, 1H), 7.60 (s, 1H), 7.37 (dt, 1H), 7.40-7.20 (m, 5H), 7.11 (s, 1H), 7.00 (s, 1H), 5.84 (s, 1H), 4.17 (t, 2H), 3.68-3.50 (m, 1H), 2.88-2.70 (m, 2H), 2.48 (t, 2H), 2.30 (s, 3H), 2.29-1.90 (m, 4H), 1.90-1.50 (m, 4H)

Example 421

5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-enylamine.

10

421A

To a solution of 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)-methyl]phenyl}pent-4-enylamine (200mg) in *N,N*-dimethylformamide (1.8mL) are added water (0.05mL), potassium hydroxide (42mg) and palladium(II) acetate. The tube is evacuated, filled with argon and sealed. After stirring at 120°C for 24h, the mixture is filtered on celite, and the solvent removed under reduced pressure. diluted with water and the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 90 / 10 / 0 to 90 / 10 / 1) to give 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-enylamine.

15

20

¹H NMR: 7.75-7.58 (m, 2H), 7.42-7.10 (m, 6H), 6.45 (d, 1H), 5.90 (s, 1H), 5.72 (dt, 1H), 3.68-3.50 (m, 1H), 2.95-2.85 (m, 2H), 2.85-2.65 (m, 2H), 2.50-2.35 (m, 2H), 2.25 (s, 3H), 2.25-1.65 (m, 8H),

25

421B 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine can be synthesized according to the procedure described in example 194.

Example 423

5 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ylamine, dioxalate

423AA solution of crude (1-{3-[benzothiazol-2-yl-(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)carbamic acid *tert*-butyl ester (289mg) in dichloromethane (3mL) and trifluoroacetic acid (2.5mL) is stirred at room temperature for
10 one night. The mixture is concentrated under reduced pressure, diluted with ethyl acetate, washed with aqueous 1N sodium hydroxide, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 95 / 5 / 0.5 to 80 / 20 / 0.5). The base is converted into its dioxalate salt in acetone to give 1-{3-[benzothiazol-2-yl(1-
15 methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ylamine, dioxalate melting at 145°C.

423B

A screw-capped tube is charged with 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (example 41, 200mg), copper(I) iodide (7mg), 2-
20 isobutyrylcyclohexanone (25mg), cesium carbonate (280mg), 3-(Boc-amino)pyrrolidine (160mg) and anhydrous *N,N*-dimethylformamide (1mL). The tube is evacuated, filled with argon and sealed. After stirring at 55°C for 4 days, the mixture is diluted with ethyl acetate, water and ammonia. After decantation, the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated
25 under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.5 to 95 / 5 / 0.5). to afford (1-{3-[benzothiazol-2-yl-(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)carbamic acid *tert*-butyl ester.

30 Example 432

432A

2-(5-{3-[(1*H*-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-pentyl)isoindole-1,3-dione

To a solution of 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}pentan-1-ol (35mg) in tetrahydrofuran are added
35 triphenylphosphine (31mg) and phthalimide (18mg). The reaction mixture is cooled to 0°C

and diethyl azodicarboxylate (31 μ L) is added. The reaction mixture is stirred at 0°C for 30 minute. The mixture is evaporated to dryness and the residue is purified by chromatography (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 95 / 5 / 0.5) to give 2-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}pentyl)isoindole-1,3-dione (example 305B).

432B

5-{3-[(1*H*-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-pentan-1-ol can be prepared according to the method described in example 150.

Preparation of starting materials

1-Bromo-3-(2-fluoroethoxy)benzene is prepared from 3-bromophenol and 2-fluoroethanol using standard Mitsunobu protocol.

1-Bromo-3-(3-fluoropropoxy)benzene is prepared from 3-bromophenol and 3-fluoropropanol using standard Mitsunobu protocol.

2-[2-(3-Bromophenoxy)ethyl]-6,6-dimethylbicyclo[3.1.1]hept-2-ene is prepared from 3-bromophenol and 2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethanol using standard Mitsunobu protocol.

Example 436 : N-(2-aminoethyl)-2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetamide ;

The compound is made from example 154 and ethylenediamine using method described in example 264. ¹H NMR: 7.68-7.48 (m, 2H), 7.35-6.95 (m, 8H), 5.89 (s, 1H), 3.83-3.50 (m, 3H), 3.50-3.35 (m, 1H), 3.25-3.10 (m, 1H), 2.82-2.62 (m, 3H), 2.59-2.45 (m, 1H), 2.26 (s, 3H), 2.24-1.95 (m, 3H), 1.92-1.50 (m, 5H).

Example 437 : N-(2-{3-[(5-fluoro-1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine.

437A

To a solution of 2-{3-[(5-fluoro-1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine (example 437B, 230mg) in acetonitrile (15mL) is added N,N'-bis-Boc-guanylpurazole (172mg) and diisopropylethylamine (1 equivalent) at room temperature. The mixture is stirred at room temperature for 3h. The solvent and volatiles are removed under reduced pressure. The residue is purified by chromatography on silica gel (gradient dichloromethane / methanol from 100 / 0 to 95 / 5).

The residue is then dissolved in 5N aqueous hydrochloric acid (8mL) and the solution is stirred overnight at room temperature. The solvent and volatiles are removed under reduced pressure and the residue is triturated with diethyl ether and filtered to afford N-(2-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine trihydrochloride as a white crystalline solid melting at 170 °C.

437B

2-{3-[(5-Fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine.

To a solution of (2-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)carbamic acid tert-butyl ester (example 437C, 386mg) in chloroform (10mL) are added phenol (750mg) and chlorotrimethylsilane (814mg). The mixture is heated at reflux for 2h. The solvent and volatiles are removed under reduced pressure. The residue is basified by adding a solution of 1N sodium hydroxide. The aqueous phase is extracted by ethyl acetate. The organic phase is washed by water, then dried over magnesium sulfate and concentrated. The residue is purified by chromatography on silica gel (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 90 / 10 / 1) to give 2-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine.

¹H NMR: 8.5-9 (sl, 1H), 7.53 (s, 1H), 7.32-7.20 (m, 5H), 7.08-6.98 (m, 1H), 5.84 (s, 1H), 3.70-3.50 (m, 1H), 3.08-3.04 (m, 2H), 3.00-2.88 (m, 2H), 2.87-2.70 (m, 2H), 2.33 (s, 3H), 2.30-1.60 (m, 8H).

437C

(2-{3-[(5-Fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)carbamic acid tert-butyl ester.

A screw-capped tube is charged with 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole (example 437D, 418mg), palladium bis(dibenzylideneacetone) (30mg), Xantphos (30mg), (2-mercaptoethyl)carbamic acid tert-butyl ester (1 equivalent), diisopropylethylamine (180µL) and 1,4-dioxane (6mL). The tube is evacuated, filled with argon and sealed. After stirring at 120°C overnight, the mixture is diluted with ethyl acetate and water and the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol from 98 / 2 to 95 / 5) to afford (2-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)carbamic acid

tert-butyl ester. ¹H NMR: 11.07 (sl, 1H), 7.69-7.59 (m, 1H), 7.39-7.36 (m, 1H), 7.30-7.15 (m, 2H), 7.04-6.91 (m, 2H), 5.83 (s, 1H), 5.30 (sl, 1H), 4.20 (s, 2H), 3.65-3.40 (m, 3H), 3.30-3.05 (m, 2H), 2.80-2.65 (m, 2H), 2.27 (s, 3H), 2.25-1.75 (m, 6H), 1.55 (s, 9H).

5 437D

2-[(3-Bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole

A mixture of (3-bromophenyl)(5-fluoro-1H-benzimidazol-2-yl)methanol (example 437E, 3.30g) and 1-methylpiperidin-4-ol (2.37g) in methanesulfonic acid (10mL) is heated overnight in a sealed tube at a temperature close to 140 °C. The mixture is cooled back to
10 room temperature, poured into water which is then made alkaline with concentrated sodium hydroxide solution. The aqueous phase is extracted with ethyl acetate. Pooled extracts are dried over magnesium sulfate, concentrated under reduced pressure. The residue is purified by column chromatography over silica gel (gradient dichloromethane/methanol / ammonia from 100 / 0 / 0 to 90 / 10 / 1) to afford 2-[(3-
15 bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole. ¹H NMR: 9.92 (sl, 1H), 7.60 (s, 1H), 7.55-6.85 (m, 6H), 5.80 (s, 1H), 3.65-3.50 (m, 1H), 2.80-2.65 (m, 2H), 2.34 (s, 3H), 2.15-1.65 (m, 6H).

437E

20 (3-Bromophenyl)(5-fluoro-1H-benzimidazol-2-yl)methanol could be synthesized using the method described in example 449B.

Example 438

438A 5-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-
25 yloxy)methyl]phenyl}pent-4-ynylamine oxalate.

A solution of 2-(5-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)isoindole-1,3-dione (example 438B, 170mg) and hydrazine hydrate (200µL) in ethanol (2.5mL) is stirred at room temperature overnight. Water is added and the aqueous phase is extracted by diethyl ether. The pooled organic
30 extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (dichloromethane / methanol / ammonia from 95 / 5 / 0.5 to 90 / 10 / 1) to afford the free base. One equivalent of oxalic acid in acetone is added to the free base to afford 5-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine oxalate as a white crystalline solid melting at 150 °C

438B 2-(5-{3-[(5-Fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)isoindole-1,3-dione.

A screw-capped tube is charged with 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole (example 437D, 418mg), PEPPSi-sono catalyst (19mg), copper (I) iodide (38mg), N-pentynylphthalimide (428mg), diethylamine (880μL) and *N,N*-dimethylformamide (1.5mL). The tube is evacuated, filled with argon and sealed. The reaction mixture is stirred at 80°C overnight. As the reaction is not completed, PEPPSi-sono catalyst (10mg) and N-pentynylphthalimide (214mg) are added, and the reaction mixture is heated at 80°C for 24h. The mixture is diluted with water and the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography (gradient dichloromethane / methanol from 98 / 2 / to 90 / 10) to give 2-(5-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)isoindole-1,3-dione. ¹H NMR: 9.65 (s, 1H), 7.84-7.65 (m, 4H), 7.54 (s, 1H), 7.48-6.95 (m, 4H), 5.84 (s, 1H), 3.90 (t, 2H, *J* = 6.9Hz), 3.65-3.50 (m, 1H), 2.85-2.70 (m, 2H), 2.52 (t, 2H, *J* = 7.0Hz), 2.32 (s, 3H), 2.28-1.50 (m, 8H).

Example	Product	General methods
439	6-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine oxalate	438
mp = 146 °C		
440	4-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine oxalate	432, 150
mp = 160 °C		
441	N-(3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propyl)guanidine, dihydrochloride	278, 432, 150
mp = 318 °C		

Example 443 :1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-one, oxalate

To a solution of oxalyl chloride (317μL) in dichloromethane (8mL) at -78°C is added DMSO (517 μL). After 15min, a solution of 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ol (example 406, 958mg) in dichloromethane (18mL) is slowly added at the same temperature. After 45min triethylamine (2mL) is added and the mixture allowed to warm to room temperature. After

hydrolysis with aqueous saturated ammonium chloride, the organic phase is dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by chromatography over silica gel(dichloromethane / methanol / ammonia 98 / 2 / 0.5) affords the pure base that is then converted into its oxalate salt in acetone to give 1-{3-
5 [benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-one, oxalate melting at 105 °C.

Example	Product	General methods
444	N-(4-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butyl)guanidine, dihydrochloride	278, 432, 150
¹ H NMR: (methanol-d ₄): 7.65-7.50 (m, 2H), 7.45 (s, 1H), 7.40-7.15 (m, 5H), 5.84 (s, 1H), 3.70-3.55 (m, 1H), 3.10 (t, 2H, <i>J</i> = 6.6Hz), 3.00-2.80 (m, 4H), 2.5-2.30 (m, 5H), 2.08-1.75 (m, 4H), 1.70-1.55 (m, 4H).		
445	5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}pentan-1-ol	359B
¹ H NMR (methanol-d ₄): 9.90 (sl, 1H), 7.75-7.70 (m, 1H), 7.42-7.35 (m, 2H), 7.32-7.15 (m, 5H), 5.84 (s, 1H), 3.70-3.48 (m, 3H), 2.89 (t, 2H, <i>J</i> = 6.6Hz), 2.80-2.62 (m, 2H), 2.24 (s, 3H), 2.15-1.42 (m, 12H).		
446	N-(2-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-N-(2,2-dimethylpropionyl)guanidine	401
¹ H NMR: 12.34 (sl; 1H), 7.51 (d, 1H, <i>J</i> = 6.75 Hz), 7.48-7.40 (m, 2H), 7.30-7.20 (m, 3H), 7.20-7.05 (m, 2H), 6.65 (sl, 1H), 5.81 (s, 1H), 3.50-3.25 (m, 3H), 3.18-3.05 (m, 2H), 2.07 (m, 3H), 2.00-1.75 (m, 4H), 1.65-1.45 (m, 2H), 1.00 (s, 9H).		
447	2-[(1-methylpiperidin-4-yloxy)(4-nitrophenyl)methyl]-1H-benzimidazole	165C,B, 210, 165D
mp = 90 °C		

Example 448 : 2-{(1-methylpiperidin-4-yloxy)[3-(pyridin-3-yloxy)phenyl]methyl}benzothiazole, oxalate
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A screw-capped tube is charged with 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole (example 41, 500mg), copper(I) iodide (9mg), 2,2,6,6-tetramethylheptane-3,5-dione (37mg), cesium carbonate (701mg), 3-hydroxypyridine (125mg), powdered 4A molecular sieves (200mg) and anhydrous *N,N*-dimethylformamide
15 (1mL). The tube is evacuated, filled with argon and sealed. After stirring at 95°C for 2

days, the mixture is diluted with ethyl acetate, water and ammonia. After decantation, the aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.5 to 95 / 5 / 0.5). to afford the pure base that is then converted into its oxalate salt in acetone to give 2-[(1-methylpiperidin-4-yloxy)[3-(pyridin-3-yloxy)phenyl]methyl} benzothiazole, oxalate melting at 78 °C.

Example 449 : 2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]-5-fluoro-1H-benzimidazole, oxalate

449A

2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]-5-fluoro-1H-benzimidazole is prepared from 3-bromophenyl(5-fluoro-1H-benzimidazol-2-yl)methanol and pyrrolidin-3-ylmethanol according to general procedures 165C and 272A. Conversion into its oxalate salt in acetone gives 2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]-5-fluoro-1H-benzimidazole, oxalate melting at 70 °C.

449B

A mixture of (3-bromophenyl)hydroxyacetic acid (3.7g) and 4-fluoro-orthophenylenediamine (2g) in 5N aqueous hydrochloric solution (3.2mL) is heated under reflux for 15h and cooled back to room temperature. The mixture is basified with concentrated sodium hydroxide and extracted with ethyl acetate. The organic phase is then dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.5 to 90 / 10 / 0.5) to afford the pure 3-bromophenyl(5-fluoro-1H-benzimidazol-2-yl)methanol.

Example 455 : 4-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]aniline.

To a solution of 2-[(1-methylpiperidin-4-yloxy)(4-nitrophenyl)methyl]-1H-benzimidazole (example 447, 200mg) in methanol (5mL) and a solution of 5N hydrochloric acid in isopropanol (0.2mL) is added 10% palladium on carbon (50mg). The flask is evacuated and filled with hydrogen (balloon) and stirred overnight at room temperature. The reaction mixture is filtered on celite and the solvents are evaporated under reduced pressure to dryness. The residual solid is triturated twice with diethyl ether and the solid is

filtered and dry to afford 4-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]aniline hydrochloride as a cream-colored solid melting at 185°C

The following example is made using the same method :

Example	Product	mp
456	4-[(1H-benzimidazol-2-yl)(piperidin-4-yloxy)methyl]aniline, hydrochloride	190°C

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The following example are made using the method of example 436

Example	Product
459	N-(2-amino-ethyl)-2-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetamide
¹ H NMR: 7.70-7.52 (m, 2H), 7.50-6.90 (m, 7H), 5.85 (s, 1H), 4.75 (s, 2H), 3.85-3.45 (m, 3H), 3.45-3.30 (m, 1H), 3.25-3.05 (m, 1H), 2.80-2.60 (m, 3H), 2.57-2.42 (m, 1H), 2.25 (s, 3H), 2.20-1.95 (m, 3H), 1.90-1.55 (m, 3H).	

Example 460 : 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}-3-trifluoromethylpyrrolidin-3-ol, oxalate

A solution of 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-one (example 443, 170mg) in tetrahydrofuran (3mL) is treated with cesium fluoride (612mg) and trifluoromethyltrimethylsilane (595μL). After stirring for 2h, the mixture is hydrolyzed with 1N aqueous hydrochloric acid for one night. The reaction mixture is then concentrated under reduced pressure and the residue purified by chromatography over silica gel (dichloromethane / methanol / ammonia 98 / 2 / 0.5) to afford the pure base that is then converted into its oxalate salt in acetone to give 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}-3-trifluoromethylpyrrolidin-3-ol, oxalate. ¹H NMR of the base (CDCl₃): 7.96 (d, 1H), 7.86 (d, 1H), 7.45-7.20 (m, 3H), 6.91 (d, 1H), 6.73 (s, 1H), 6.51 (d, 1H), 5.85 (s, 1H), 3.77-3.30 (m, 5H), 2.69 (m, 2H), 2.36 (m, 1H), 2.25 (s, 3H), 2.20-1.70 (m, 7H).

Example 468 : 2-[[3-(4,5-dihydro-1H-imidazol-2-ylmethylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole.

To a solution of triphenylphosphine oxide (2.2 mmoles) in 4mL CH₂Cl₂ cooled at 0°C is added dropwise trifluoromethanesulfonyl anhydride (310 mg, 1.1 mmoles). The reaction mixture is stirred at 0°C for 30 minutes, then a solution of N-(2-aminoethyl)-2-{3-

[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetamide
 (Example 436) (250 mg, 0.55 mmole) in 2mL CH₂Cl₂ is added dropwise. The reaction
 mixture is allowed to reach room temperature and stirred for 1.5h. The organic phase is
 washed with 1N sodium hydroxide solution, then dried over magnesium sulfate and
 concentrated. The residue is purified by chromatography on silica gel (gradient
 dichloromethane / methanol / ammonia from 100 / 0 / 0 to 80 / 20 / 2). The residue is then
 dissolved in acetone and one equivalent of oxalic acid is added. Acetone is removed
 under reduced pressure to afford 2-[[3-(4,5-dihydro-1H-imidazol-2-
 ylmethylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole melting at
 62°C (déc.) ; MS, [M+H]⁺ = 436.1.

The following example is made using the same method

Example	Product	mp
463	2-[[3-(4,5-dihydro-1H-imidazol-2-ylmethylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole	80°C

Example 469 : 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5,6-difluoro-1H-benzimidazole

469A

2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5,6-difluoro-1H-benzimidazole is prepared from 3-bromophenyl(5,6-difluoro-1H-benzimidazol-2-yl)methanol according to general procedure 272A, solid melting at 70°C.

469B

A mixture of (3-bromophenyl)hydroxyacetic acid (809mg) and 4,5-difluoro-ortho-phenylenediamine (500mg) in 5N aqueous hydrochloric solution (2mL) is heated under reflux for 15h and cooled back to room temperature. The mixture is basified with concentrated sodium hydroxide and extracted with ethyl acetate. The organic phase is then dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by trituration in dichloromethane to afford the pure 3-bromophenyl(5,6-difluoro-1H-benzimidazol-2-yl)methanol.

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Example 472 : 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1-methyl-1H-benzimidazole, dioxalate

A solution of 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole (example 51, 260mg) in anhydrous acetonitrile (10mL) is treated with 60% sodium hydride (47mg) for 1h at room temperature. The mixture is then cooled to 0°C and iodomethane (36μL) is introduced. After stirring for 15h, dilution with water and extraction with ethyl acetate, the organic phase is dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol / ammonia from 95 / 5 / 0.5 to 90 / 10 / 0.5) to afford the pure base that is then converted into its dioxalate salt in acetone to give 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1-methyl-1H-benzimidazole, dioxalate, melting at 76°C.

Example 479 : 2-amino-5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-1,5-dihydroimidazol-4-one

479A 2-amino-5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-1,5-dihydroimidazol-4-one.

To a solution of 3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-2-(N,N'-bis-tert-butoxycarbonyl)guanidinopropionic acid methyl ester (260mg) in dichloromethane (2.6mL) is added dropwise trifluoroacetic acid (1mL). The reaction mixture is stirred at room temperature for 28h. Solvents are removed under reduced pressure. The residue is basified by adding 1N sodium hydroxide, and the solution is evaporated to dryness. The residue is purified by chromatography on silica gel (gradient dichloromethane / methanol / ammonia from 90 / 10 / 0 to 90 / 10 / 1). The residual solid is triturated in hot ethyl acetate, cooled down to room temperature and filtered. The solid is washed with ethyl acetate; then dried to afford 2-amino-5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-1,5-dihydroimidazol-4-one.

MS, $[M+H]^+ = 465.1$; $[M+Na]^+ = 487.1$.

479B

3-{3-[(1H-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-2-(N,N'-bis-tert-butoxycarbonyl)guanidinopropionic acid methyl ester.

The compound is synthesized from Example 479C using the method described at example 307A ; mixture of diastereomers. ^1H NMR: 11.35 and 11.13 (sl, 1H), 10.25 and 10.06 (sl, 1H), 9.04 and 8.90 (d, 1H, $J = 7.5Hz$), 7.82-7.70 (m, 2H), 7.52-7.18 (m, 6H), 5.89 and 5.84 (s, 1H), 5.58-5.30 (m, 1H), 5.25-5.90 (m, 1H), 4.65-4.40 (m, 1H), 3.82-3.05 (m, 6H), 2.95-2.75 (m, 2H), 2.38 (sl, 3H), 2.252-1.60 (m, 6H), 1.60-1.30 (m, 18H).

479C

2-Amino-3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propionic acid methyl ester.

The compound is synthesized from example 479D using the method described in example 437B ; mixture of diastereomers. ¹H NMR: 9.74 and 9.67 (sl, 1H), 7.80-7.55 (m, 2H), 7.48-7.15 (m, 7H), 5.84 (s, 1H), 3.75-3.50 (m, 3H), 3.42-3.15 (m, 3H), 2.90-2.70 (m, 2H), 2.40-2.15 (m, 5H), 2.10-1.70 (m, 6H).

479D

3-{3-[(1H-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-2-tert-butoxycarbonylaminopropionic acid methyl ester.

The compound is synthesized from 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole (example 72A) and N-Boc-Cysteine methyl ester using the method described in example 150 ; mixture of diastereomers. ¹H NMR: 10.66 and 9.83 (sl, 1H), 7.90-7.70 (m, 2H), 7.50-7.35 (m, 2H), 7.35-7.18 (m, 5H), 5.87 and 5.85 (s, 1H), 5.58-5.30 (m, 1H), 4.65-4.40 (m, 1H), 3.70-3.20 (m, 6H), 2.82-2.62 (m, 2H), 2.28 and 2.26 (s, 3H), 2.22-1.65 (m, 6H), 1.53 and 1.45 (s, 9H).

Example 481 : 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5,6,7-trifluoro-1H-benzimidazole

481A

2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5,6,7-trifluoro-1H-benzimidazole, solid melting at 140 °C, is prepared according to general procedure 165C from 2-[(3-bromophenyl)(piperidin-4-yloxy)methyl]-5,6,7-trifluoro-1H-benzimidazole.

481B

To a solution of 4-[(3-bromophenyl)carboxymethoxy]piperidine-1-carboxylic acid tert-butyl ester (general procedure 165D + saponification)(1g) in acetonitrile (10mL) are added 3,4,5-trifluorobenzene-1,2-diamine (470mg), 2-chloro-1-methylpyridinium iodide (802mg) and dropwise diisopropylethylamine (1.1mL). The reaction mixture is stirred at room temperature for 2 hours. Solvent is removed under reduced pressure and the residue diluted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1) to get 4-[(6-amino-2,3,4-trifluorophenyl)carbonyl](3-

bromophenyl)methoxy]piperidine-1-carboxylic acid tert-butyl ester. This intermediate is dissolved in acetic acid (15mL) and the reaction mixture is refluxed for 3 hours. Acetic acid is removed under reduced pressure. Water is added to the residue and the solution is basified by adding a solution of saturated sodium hydrogencarbonate to pH 10. The aqueous phase is extracted with ethyl acetate. The pooled organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.2 to 90 / 10 / 1) to yield 2-[(3-bromophenyl)(piperidin-4-yloxy)methyl]-5,6,7-trifluoro-1H-benzimidazole.

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Example 497 : 1-(2-ethoxyethyl)-2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, dioxalate

A solution of 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole (example 51, 260mg) in anhydrous acetonitrile (10mL) is treated with 60% sodium hydride (47mg) for 30 min at room temperature. 1-Bromo-2-ethoxyethane (84µL) is then introduced. After warming at 60°C for 8h, dilution with water and extraction with diethylether, the organic phase is dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol / ammonia from 98 / 2 / 0.5 to 95 / 5 / 0.5) to afford the pure base that is then converted into its dioxalate salt in acetone to give 1-(2-ethoxyethyl)-2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, dioxalate, melting at 88°C.

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Example 505

505A : 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzylidene}-2-iminoimidazolidin-4-one.

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To a solution of 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-benzaldehyde (example 505C, 200mg) in a mixture of ethanol-water (8 : 2) (3mL) is added thiohydantoin (70mg) and piperidine (57µL). The reaction mixture is heated at 55°C for 5h. Ethanol is removed under reduced pressure. Water is added and the reaction mixture is extracted by ethyl acetate. The organic phase is washed by water, then dried over magnesium sulfate and concentrated. The residue is purified by chromatography on silica gel (gradient dichloromethane / methanol from 95 / 5 to 90 / 10). The residue is dissolved in methanol (6mL) and 30% solution of aqueous ammonia (1.1mL) and *tert*-butylhydroperoxide (90µL) are added. The reaction mixture is stirred at room temperature for two days. The reaction mixture is evaporated to dryness. The residue is purified by

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chromatography on silica gel (gradient dichloromethane / methanol / ammonia from 90 / 10 / 0.1 to 70 / 30 / 0.1) to give 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzylidene}-2-iminoimidazolidin-4-one. MS, $[M+H]^+ = 431.1$; $[M+Na]^+ = 453.1$

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505B

3-[(1H-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzaldehyde.

To a solution of 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzonitrile (example 172, 740mg) in 80% aqueous formic acid (3mL) is added platinum(IV) oxide (48mg). The reaction mixture is heated at 60°C for 7h, then at room temperature for 2 days. As the reaction is not complete, 80% aqueous formic acid (3mL) and platinum (IV) oxide (48mg) are added and the reaction mixture is heated at 60°C overnight. Water is added and the reaction mixture is filtered on celite. The phase is basified by adding a solution of 1N sodium hydroxide and extracted by ethyl acetate. The organic phase is washed by water, then dried over magnesium sulfate and concentrated to give 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzaldehyde. ¹H NMR: 9.99 (s, 1H), 9.67 (sl, 1H), 8.01 (s, 1H), 7.85-7.65 (m, 2H), 7.60-7.40 (m, 2H), 7.32-7.15 (m, 3H), 5.95 (s, 1H), 3.65-3.50 (m, 1H), 2.82-2.65 (m, 2H), 2.26 (s, 3H), 2.20-1.65 (m, 6H).

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Example 507 : 4-{3-[(1H-benzimidazol-2-yl)(1-methylazetidin-3-ylmethoxy)methyl]phenylsulfanyl}butylamine, oxalate. Compound made from example 506 using methods described in examples 150, 432. ¹H NMR (methanol-d₄)(base) : 7.65-7.40 (m, 3H), 7.40-7.10 (m, 5H), 5.69 (s, 1H), 3.785-3.40 (m, 4H), 3.40-3.10 (m, 5H), 2.44 (s, 3H), 1.80-1.45 (m, 3H), 1.35-1.10 (m, 2H), 1.00-1.75 (m, 1H).

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Example 525 : 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzoxazole, oxalate

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525A

2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzoxazole, oxalate (solid melting at 103°C) is prepared according to general procedure 272A.

525B

A mixture of (2-fluoro-5-trifluoromethoxyphenyl)hydroxyacetic acid (prepared according to 72C) (2.4g), ortho-aminophenol (1.03g) in xylene (25mL) is refluxed for 4h with a Dean-Stark apparatus and concentrated under reduced pressure. Purification by chromatography on silica gel (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 98 / 2 / 0.5) to afford the pure benzoxazol-2-yl(2-fluoro-5-trifluoromethoxyphenyl)methanol.

10 Example 528

528A

2-[(1-methylpiperidin-4-yloxy)(3-methylsulfanylmethylphenyl)methyl]-1H-benzimidazole.

To a solution of {3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}methanol (example 528B, 320mg) in dichloromethane (3mL) is added triethylamine (0.16mL). The reaction mixture is cooled to 0°C, and methanesulfonyl chloride (84µL) is added dropwise. The reaction mixture is stirred at room temperature for 3h, then cooled to 0°C and sodium thiomethoxide (191mg) is added. After one night at room temperature, methanol (2mL) is added to help solubilizing the suspension. The reaction mixture is stirred at room temperature overnight. Water is added and the aqueous phase is extracted by dichloromethane. The organic phase is washed by water, then dried over magnesium sulfate and concentrated. . The residue is purified by chromatography on silica gel (gradient dichloromethane / methanol / ammonia from 90 / 10 / 0 to 90 / 10 / 0.1 then 80 / 20 / 0.1), followed by a purification by preparative thin-layer chromatography (dichloromethane / methanol / ammonia from 90 / 10 / 0.1) to give 2-[(1-methylpiperidin-4-yloxy)(3-methylsulfanylmethylphenyl)methyl]-1H-benzimidazole. MS, [M+H]⁺ = 382.1 ;

528B

{3-[(1H-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}methanol.

To a solution of 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzaldehyde (example 505B, 310mg) in methanol (4mL) is added portionwise sodium borohydride (50mg). The reaction mixture is stirred at room temperature for 15 minutes then heated at reflux for 3h. Methanol is removed under reduced pressure. Water is added and the aqueous phase is extracted by ethyl acetate. The organic phase is washed by water, then dried over magnesium sulfate and concentrated to give {3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-

phenyl}methanol. ¹H NMR: 9.85 (sl, 1H), 7.78-7.65 (m, 1H), 7.50-7.12 (m, 7H), 5.87 (s, 1H), 4.64 (s, 2H), 3.62-3.45 (m, 1H), 2.78-2.58 (m, 2H), 2.22 (s, 3H), 2.15-1.50 (m, 6H).

Example 530

5 530A 2-[(3-bromophenyl)(1-methyl-1,2,3,6-tetrahydropyridin-4-ylsulfanyl)methyl]-1H-benzimidazole.

To a solution of 1,2-phenylenediamine (213mg) in toluene (2mL) is added dropwise a solution of 2M trimethylaluminium in toluene (1ml). The reaction mixture is heated at 75°C for 2 hours then a solution of (3-bromophenyl)(1-methyl-1,2,3,6-tetrahydropyridin-4-ylsulfanyl)acetic acid methyl ester (example 530B, 358mg) in toluene (2mL) is added, and the heating is continued at 75°C for 3 hours. Water is added and the reaction mixture is made alkaline by adding 1N sodium hydroxide. The aqueous phase is extracted by ethyl acetate. The organic phase is washed by water, brine, then dried over magnesium sulfate and concentrated. The residue is dissolved in acetic acid (5mL) and the reaction mixture is refluxed for 3 hours. The solvent is removed under reduced pressure. Water is added and the reaction mixture is made alkaline by adding 2N sodium hydroxide. The aqueous phase is extracted by ethyl acetate. The organic phase is washed by water, brine, then dried over magnesium sulfate and concentrated. The residual solid is triturated with acetonitrile, filtered and the solid is washed with diethyl ether to give 2-[(3-bromophenyl)(1-methyl-1,2,3,6-tetrahydropyridin-4-ylsulfanyl)methyl]-1H-benzimidazole melting at 189°C.

530B

(3-Bromophenyl)(1-methyl-1,2,3,6-tetrahydropyridin-4-ylsulfanyl)acetic acid methyl ester

To a solution of 4-[(3-bromophenyl)methoxycarbonylmethylsulfanyl]-1-methylpyridinium iodide (example 530C, 480mg) in methanol (5mL) is added portionwise sodium borohydride (2 equivalents). The mixture is refluxed for one hour then concentrated to dryness. Water is added and the aqueous phase is extracted by ethyl acetate. The organic phase is washed by water, brine, then dried over magnesium sulfate and concentrated to give (3-Bromophenyl)(1-methyl-1,2,3,6-tetrahydropyridin-4-ylsulfanyl)acetic acid methyl ester. ¹H NMR: 7.62 (s, 1H), 7.50-7.35 (m, 2H), 7.30-7.15 (m, 1H), 5.75 (sl, 1H), 4.77 (s, 1H), 3.76 (s, 3H), 3.10-2.98 (m, 2H), 2.68-2.55 (m, 2H), 2.45-2.25 (m, 5H).

530C

4-[(3-Bromophenyl)methoxycarbonylmethylsulfanyl]-1-methylpyridinium iodide.

To a solution of (3-bromophenyl)(pyridin-4-ylsulfanyl)acetic acid methyl ester (example 530D, 2.2g) in acetonitrile (50mL) is added iodomethane (1.2 equivalent) and the mixture is stirred over-the-weekend at room temperature. The solid is filtered and washed with diethyl ether to give 4-[(3-Bromophenyl)methoxycarbonylmethylsulfanyl]-1-methylpyridinium iodide. ¹H NMR (dmso-d₆): 8.75-8.65 (m, 2H), 7.98-7.88 (m, 2H), 7.78 (s, 1H), 7.63-7.51 (m, 2H), 7.42-7.30 (m, 1H), 6.20 (s, 1H), 4.13 (s, 3H), 3.70 (s, 3H).

10 530D

(3-Bromophenyl)(pyridin-4-ylsulfanyl)acetic acid methyl ester

To a solution of dimethylsulfoxonium ylide and 3-bromophenylacetic acid methyl ester (example 530E, 3g) in dichloroethane (50mL) are added 4-mercaptopyridine (2 equivalents) and [Ir(COD)Cl]₂ (20mg). The reaction mixture is refluxed overnight then concentrated to dryness under reduced pressure. The residue is purified by chromatography on silica gel (heptane / ethyl acetate 1 /1) to give (3-Bromophenyl)(pyridin-4-ylsulfanyl)acetic acid methyl ester. ¹H NMR: 8.50-8.35 (m, 2H), 7.68 (s, 1H), 7.55-7.45 (m, 2H), 7.35-7.20 (m, 1H), 7.20-7.05 (m, 2H), 5.08 (s, 1H), 3.77 (s, 3H).

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530E

Dimethylsulfoxonium ylide of 3-Bromophenylacetic acid methyl ester

To a solution of (3-bromophenyl)diazoacetic acid methyl ester (synthesized according to the method described in example 165E, 7.5g) in dimethylsulfoxide (35mL) is added copper(II)cyanide (150mg), and the mixture is heated at 60°C for 1h, with evolution of nitrogen. The solvent is removed under reduced pressure. Water is added and the reaction mixture is extracted by ethyl acetate. The organic phase is washed by water, brine, then dried over magnesium sulfate and concentrated. The residual solid is triturated with diisopropyl ether, filtered and dried to give the dimethylsulfoxonium ylide of 3-bromophenylacetic acid methyl ester. ¹H NMR: 7.47 (s, 1H), 7.45-7.35 (m, 1H), 7.30-7.12 (m, 2H), 3.63 (s, 3H), 3.45 (s, 6H)

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Example 533 2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer B

A solution of racemic 2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole (10mg/mL) in a mixture of heptane / isopropanol (90 / 10)

35

containing diethylamine (0.1%) is injected (30x100 μ L) onto an analytical Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. Products are detected at 210nm. The enantiomer B has a retention time of 13.2min. Collection affords 2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole enantiomer B with a chromatographic enantiomeric purity of 97.4%.

Example 534 : 2-[(2,6-difluoro-3-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole

10 534A

2-[(2,6-Difluoro-3-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole (solid melting at 185 °C) is prepared according to general procedure 172A from (1H-benzimidazol-2-yl)(2,6-difluoro-3-methoxyphenyl)methanol.

15 534B

A solution of (2,6-difluoro-3-methoxyphenyl)[1-(2-trimethylsilylethoxymethyl)-1H-benzimidazol-2-yl]methanol (1.4g) in tetrahydrofuran (20mL) is refluxed for 15h with tetrabutylammonium fluoride (10mL of a 1M solution in tetrahydrofuran). The mixture is then concentrated under reduced pressure and purified by chromatography over silica gel (gradient dichloromethane / methanol from 100 / 0 to 95 / 5) to afford the pure (1H-benzimidazol-2-yl)-(2,6-difluoro-3-methoxyphenyl)methanol.

534C

To a solution of 2,4-difluoro-1-methoxybenzene (156mg) in tetrahydrofuran (5mL) at -78 °C is added a 2M solution of lithium diisopropylamide in THF (540 μ L). After stirring for 45min a solution of 1-(2-trimethylsilylethoxymethyl)-1H-benzimidazole-2-carbaldehyde (which can be prepared according to US2003/220341 or US6476041 for example) (300mg) in tetrahydrofuran (5mL) is added at -78 °C and the reaction mixture allowed to warm to room temperature. After hydrolysis with aqueous saturated ammonium chloride and extraction with ethyl acetate, the organic phase is dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol from 100 / 0 to 95 / 5) to afford (2,6-difluoro-3-methoxyphenyl)[1-(2-trimethylsilylethoxymethyl)-1H-benzimidazol-2-yl]methanol.

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Example 549 : ethyl (6-{3-[(1-methyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)carbamate, oxalate

To a cooled solution of 6-{3-[(1-methyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine (example 480, 22mg) in dichloromethane is added
5 ethyl chloroformate (1eq). After stirring at room temperature, the organic phase is washed with aqueous sodium hydroxide, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol from 100 / 0 to 90 / 10) to afford the pure base that is then
10 converted into its oxalate salt in acetone to give ethyl (6-{3-[(1-methyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)carbamate, oxalate melting at 90°C.

Example 550 : 2-[(1H-indol-6-yl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate

15 550A

2-[(1-Benzenesulfonyl-1H-indol-6-yl)(1-methyl-piperidin-4-yloxy)methyl]-1H-benzimidazole (150mg) and sodium hydroxide (excess) in methanol are refluxed for 3h. The reaction mixture is then concentrated under reduced pressure, diluted with water and extracted with dichloromethane. The organic phase is dried over magnesium sulfate and
20 concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 80 / 20 / 2) to afford the pure base that is then converted into its oxalate salt in acetone to give 2-[(1H-indol-6-yl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate, melting at 170°C.

25 550B

2-[(1-Benzenesulfonyl-1H-indol-6-yl)(1-methyl-piperidin-4-yloxy)methyl]-1H-benzimidazole is prepared according to general procedures 172A and 172B from 1-benzenesulfonyl-1H-indole-6-carbaldehyde.

30 Example 556 : 2-[benzo[b]thiophen-6-yl(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate

556A

2-[Benzo[b]thiophen-6-yl(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole,
35 oxalate melting at 160°C is prepared according to general procedures 272A and 534B

from benzo[b]thiophen-6-yl[1-(2-trimethylsilylethoxymethyl)-1H-benzimidazol-2-yl]methanol.

556B

5 To a suspension of magnesium (86mg) in tetrahydrofuran is added a solution of 6-bromobenzo[b]thiophene (which can be prepared according to WO2006/107784) (500mg) in tetrahydrofuran. After reflux for 3h, a solution of 1-(2-trimethylsilylethoxymethyl)-1H-benzimidazole-2-carbaldehyde (which can be prepared according to US2003/220341 or US6476041 for example) (635mg) in tetrahydrofuran is added to the Grignard reagent at
10 room temperature. After stirring for 12h, the reaction mixture is treated with diluted hydrochloric acid and the organic phase is dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol from 100 / 0 to 90 / 10) to afford benzo[b]thiophen-6-yl[1-(2-trimethylsilylethoxymethyl)-1H-benzimidazol-2-yl]methanol.

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Example 559 : 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer B

A solution of racemic 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole (example 523) (10mg/mL) in a mixture of heptane /
20 isopropanol (90 / 10) containing diethylamine (0.1%) is injected (30x100µL) onto an analytical Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. Products are detected at 210nm. The enantiomer B has a retention time of 13.9min. Collection affords 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-
25 benzimidazole, enantiomer B with a chromatographic enantiomeric purity of 99.3%

Example 561 : 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol
561A

2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol (solid melting at
30 118-120°C) is prepared from 2-[(1H-benzimidazol-2-yl)hydroxymethyl]phenol according to general procedure 1A.

561B

To a solution of 1-pyrrolidin-1-ylmethyl-1H-benzimidazole (6g) in tetrahydrofuran
35 (40mL) at -78°C, is added a 2.3M solution of butyllithium in hexanes (13mL). The mixture is stirred for 25 minutes. Salicylaldehyde (1.82g) is then dropwise introduced at -78°C. After

1h at the same temperature, the mixture is allowed to warm to room temperature and hydrolyzed with aqueous saturated ammonium chloride. After 1h, the mixture is extracted with ethyl acetate. Pooled extracts are washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by titration in
5 dichloromethane to afford 2-[(1H-benzimidazol-2-yl)hydroxymethyl]phenol.

Example 562 : 2-[(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylimino)phenylmethyl]phenol

A mixture of 6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylamine, oxalate (example 557, 70mg), 2-hydroxybenzophenone
10 (30mg) in ethanol (4mL) is refluxed for 4h. The mixture is then cooled, diluted with water and extracted with ethyl acetate. Pooled extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0 to 90 / 10 / 0.5)
15 to afford 2-[(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylimino)phenylmethyl]phenol. TLC (Eluent: CH₂Cl₂/MeOH/NH₄OH 95/5/0.5) R_f=0.15.

Example 563 : 5-(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylimino)-2-methylcyclopent-1-enol
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A mixture of 6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylamine, oxalate (example 557, 50mg), 3-methyl-1,2-cyclopentanedione (11.8mg) in ethanol (2mL) is refluxed for 2h. The mixture is then cooled, diluted with water and 1N sodium hydroxide and extracted with ethyl acetate.
25 Pooled extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0.5 to 95 / 5 / 0.5) to afford 5-(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylimino)-2-methylcyclopent-1-enol. TLC (Eluent: CH₂Cl₂/MeOH/NH₄OH 95/5/0.5)
30 R_f=0.30.

Example 564 : 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer B

Resolution of racemic 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole (example 78) with (1R)-(-)-10-camphorsulfonic acid (0.45eq) in ethyl
35 acetate affords after several recrystallizations enantiopure 2-[(3-bromophenyl)(1-

methyloxy)methyl]-1H-benzimidazole, enantiomer B (solid melting at 85°C). HPLC analysis: analytical Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. The enantiomer B has a retention time of 10.4min.

5

Example 565 : 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine, enantiomer A

5-{3-[(1H-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine, enantiomer A (melting at 84°C) is prepared according to general procedures 194 and 189 from 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer A (prepared according example 564 with (1S)-(+)-camphorsulfonic acid).

Example 566 : 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine, enantiomer B

5-{3-[(1H-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine, enantiomer B (melting at 82°C) is prepared according to general procedures 194 and 189 from 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer B (example 564).

20

Example 567 : 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole, enantiomer A

Resolution of racemic 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole with (1S)-(+)-10-camphorsulfonic acid (0.5eq) in ethyl acetate affords after several recrystallizations 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole, enantiomer A (solid melting at 89°C). HPLC analysis: analytical Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. The enantiomer A has a retention time of 8.2min. e.e.=93.5%

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Example 568 : 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole, enantiomer B

Resolution of racemic 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole with (1R)-(-)-10-camphorsulfonic acid (0.5eq) in ethyl acetate affords after several recrystallizations 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole, enantiomer B (solid melting at 89°C). HPLC

35

analysis: analytical Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. The enantiomer B has a retention time of 10.3min. e.e.=95.5%

5 Example 578 : 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-methylphenol

A mixture of 2-[(1H-benzimidazol-2-yl)hydroxymethyl]-4-methylphenol (prepared according to procedure 561B) (360mg), methanesulfonic acid (500μL) and 1-methyl-4-piperidinol (500mg) in 1,2-dichloroethane (20mL) and N-methylpyrrolidinone (2mL) is
10 warmed at 90°C for 2h. After cooling at 0°C, the mixture is diluted with water and dichloromethane and concentrated sodium hydroxide slowly added up to pH 9. Organic phase is then dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by chromatography over silica gel (gradient dichloromethane / methanol / ammonia from 100 / 0 / 0.5 to 80 / 20 / 0.5) to afford 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-methylphenol, melting at 151°C.
15

For the other examples prepared according this general procedure, it can be advantageous to rise the temperature progressively after having mixed the different reagents and to observe when etherification occurs. Once the right temperature has been found, reaction may be continued up to adequate conversion. Use of N-methylpyrrolidinone can be optional depending of the solubility of the mixture. Additional
20 equivalents of methanesulfonic acid can be used for a better conversion if necessary.

Example 626: 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol enantiomer A

25 2-[(1H-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol enantiomer A is prepared by separation on Chiralpak AD-H from racemic 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol (example 561). HPLC analysis: Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. The enantiomer A has a retention
30 time of 18.8min. e.e.=100%

Example 627 : 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol enantiomer B

2-[(1H-Benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol enantiomer B is
35 prepared by separation on Chiralpak AD-H from racemic 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol (example 561). HPLC analysis: Chiralpak AD-H,

250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. The enantiomer B has a retention time of 34.3min. e.e.=100%

5 Example 628 : 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol enantiomer A

By analogy with example 626 from racemic 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol (example 601). HPLC analysis: Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. The enantiomer A has a retention time of 15.8min.

Example 629 : 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol enantiomer B

15 By analogy with example 627 from racemic 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol (example 601). HPLC analysis: Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. The enantiomer B has a retention time of 19.9min.

20

Example 630 : 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol enantiomer A

By analogy with example 626 from racemic 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol (example 625). HPLC analysis: Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. The enantiomer A has a retention time of 13.4min.

30 Example 631 : 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol enantiomer B

By analogy with example 627 from racemic 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol (example 625). HPLC analysis: Chiralpak AD-H, 250x4.6 mm column. Elution is performed with a mixture of heptane / isopropanol (90 / 10) containing diethylamine (0.1%) at a flow of 1mL/min. The enantiomer B has a retention time of 15.3min.

35

Further examples can be prepared according to the described general methods:

Example	Product	General methods	Melting point
442	5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}pent-4-ynylamine, dioxalate	194, 189, 425	139 °C
453	3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}cyclopentylamine, oxalate	194, 432A, 258	91 °C
454	2-{[3-(3-fluoropyrrolidin-1-yl)phenyl](1-methylpiperidin-4-yloxy)methyl}benzothiazole, oxalate	423B	103 °C
462	5-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpyrrolidin-3-ylmethoxy)methyl]phenyl}pent-4-ynylamine, oxalate	194, 189, 449	200 °C
464	2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]benzothiazole, oxalate (one epimer)	165C, 1A, 1B	68 °C
465	2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]benzothiazole, oxalate (50/50 mixture of two epimers)	165C, 1A, 1B	68 °C
466	2-{(1-methylpiperidin-4-yloxy)[3-(octahydrocyclopenta[c]pyrrol-5-yloxy)phenyl]methyl}benzothiazole, dioxalate	249, 258	70 °C
467	(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)methylamine, dioxalate	249, 423B	216 °C
470	4-{3-[(5,6-difluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol	150, 469	60 °C
471	2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}octahydrocyclopenta[c]pyrrol-5-ylamine, dioxalate	194, 432A, 423B	126 °C
475	2-{[3-(3-fluoropropoxy)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, oxalate	272A, 272B	106 °C

476	2-{[3-(2-fluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole,oxalate	272A, 272B	136 °C
477	4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}cyclohexylamine, oxalate	194, 432A, 258	95 °C
480	6-{3-[(1-methyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine, dioxalate	194, 189, 472	113 °C
482	1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-2-ylmethylamine, oxalate	194, 432A, 423B	145 °C
483	(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)(methyl)amine, oxalate	249, 423B	115 °C
484	(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)(dimethyl)amine, oxalate	423B	106 °C
485	2-{[3-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2-yl)phenyl](1-methylpiperidin-4-yloxy)methyl}benzothiazole, dioxalate	423B	131 °C
486	2-[(2-fluoro-5-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate	272A, 272B	105 °C
487	3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenol, oxalate	272A, 272B	135 °C
489	2-{[2-fluoro-5-(2-fluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, oxalate	272A, 272B	109 °C
490	2-[(2-fluoro-5-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate	272A, 272B	132 °C
493	4-{3-[(1-methylpiperidin-4-yloxy)(5,6,7-trifluoro-1H-benzimidazol-2-yl)methyl]phenylsulfanyl}butylamine, oxalate	305A, 305B, 481	110 °C
495	4-{3-[(5,6-difluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine, oxalate	305A, 305B, 469	180 °C

500	6-(3-{{1-(2-ethoxyethyl)-1H-benzimidazol-2-yl}}(1-methylpiperidin-4-yloxy)methyl}phenyl)hex-5-ynylamine, dioxalate	194, 189, 497	103 °C
501	6-(3-{{1-(2-methoxyethyl)-1H-benzimidazol-2-yl}}(1-methylpiperidin-4-yloxy)methyl}phenyl)hex-5-ynylamine, dioxalate	194, 189, 497	109 °C
508	2-{{3-(3-fluoropropylsulfanyl)phenyl}}(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, dioxalate	150	85 °C
509	5-fluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate	272A, 272B	70 °C
510	4,5,6-trifluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	75 °C
511	5,6-difluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	79 °C
522	2-{{2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl}}(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	204 °C
523	2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	211 °C
524	2-[(2-chloro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate	272A, 272B	107 °C
526	2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	272A, 1B	95 °C
527	2-[(4-chloro-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	195 °C
529	7-fluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate	165C, 165A	135 °C
531	2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	272A, 168B	125 °C

532	2-[(4-chloro-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate	272A, 1B	158 °C
535	2-[(3-ethoxy-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	534	130 °C
536	2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzoxazole, oxalate	525	114 °C
537	2-[(1-methylpiperidin-4-yloxy)(4-trifluoromethylphenyl)methyl]-1H-benzimidazole	272A, 272B	86 °C
540	2-[(2-fluoro-4-trifluoromethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	91 °C
541	2-[(2,4-dimethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	120 °C
542	2-[(3-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	83 °C
543	2-[chroman-7-yl(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	128 °C
545	2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzoxazole, oxalate	525	110 °C
547	2-[(3,5-bis-trifluoromethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate	272A, 272B	130 °C
548	5-fluoro-2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	90 °C
551	2-[(2,3-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	80 °C
552	2-[(3-chloro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	86 °C
553	ethyl 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzimidazole-1-carboxylate, oxalate	549	118 °C
554	2-[(3-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	92 °C
555	2-[(5-bromo-2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 272B	232 °C

557	6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylamine, oxalate	194, 189, 555	195 °C
558	5-{4-fluoro-3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine	194, 189, 272A, 272B	90 °C
560	ethyl (5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}pent-4-ynyl)carbamate	549, 442	87 °C
569	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-chlorophenol	272A, 561B	185 °C
570	ethyl (5-{4-fluoro-3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)carbamate	189, 272A, 272B	95 °C
571	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-trifluoromethoxyphenol	272A, 561B	132 °C
572	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenol	272A, 561B	142 °C
573	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-methoxyphenol	1A, 561B	146 °C
574	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-methylphenol	1A, 561B	145 °C
575	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-bromophenol	272A, 561B	145 °C
576	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-ethoxyphenol	272A, 561B	213 °C
577	2-[(1H-indol-7-yl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	550A, 1A, 272B	110 °C
579	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,6-difluorophenol	272A, 561B	142 °C
580	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,6-dichlorophenol	272A, 561B	161 °C
581	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-fluorophenol	578	145 °C

582	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-fluorophenol	578	129 °C
583	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,5-difluorophenol	272A, 561B	198 °C
584	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-fluorophenol	578	140 °C
585	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-chlorophenol	578	142 °C
586	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-methylphenol	578	111 °C
587	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-methylsulfanylphenol	578	138 °C
588	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-ethylsulfanylphenol	578	116 °C
589	3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-ol	578	140 °C
590	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-tert-butylphenol	272A, 561B	139 °C
591	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-propylphenol	578	120 °C
592	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-methoxyphenol	578	112 °C
593	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-fluoro-5-methylphenol	578	136 °C
594	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-chlorophenol	272A, 561B	145 °C
595	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-fluoro-4-methylphenol	272A, 561B	144 °C
596	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-benzylphenol	272A, 561B	120 °C
598	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-trifluoromethylphenol	578	135 °C
599	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-chloro-6-fluorophenol	272A, 561B	146 °C

600	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-3-methylphenol	272A, 561B	146 °C
601	6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol	272A, 561B	148 °C
602	6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]indan-5-ol	578	152 °C
603	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-propoxyphenol	578	120 °C
604	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(1-methyl-1-phenylethyl)phenol	272A, 561B	130 °C
605	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(2-fluoroethoxy)phenol	578	222 °C
606	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(3-fluoropropoxy)phenol	578	114 °C
607	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluoro-6-methylphenol	272A, 561B	111 °C
608	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-fluoro-4-methoxyphenol	272A, 561B	132 °C
609	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-phenoxyphenol	578	140 °C
610	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluoro-6-methoxyphenol	578	108 °C
611	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,5-dimethylphenol	578	139 °C
612	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(3-fluoropropylsulfanyl)phenol	578	128 °C
613	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluoro-5-methylphenol	1A, 561B	102 °C
614	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(2-fluoroethylsulfanyl)phenol	578	127 °C
615	3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-hydroxybiphenyl	578	129 °C
616	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-ethylphenol	578	105 °C

617	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-trifluoromethylphenol	272A, 561B	144 °C
618	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-hydroxyphenol	1A, 561B	189 °C
619	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5,6,7,8-tetrahydro-1-naphthol	578	125 °C
620	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-trifluoromethoxyphenol	578	126 °C
621	2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-trifluoromethoxyphenol	578	133 °C
622	6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3,4-dimethylphenol	578	163 °C
623	6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-fluoro-2-methylphenol	578	97 °C
624	6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,4-difluoro-3-methylphenol	578	146 °C
625	6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol	578	184 °C

Further examples can be prepared according to the described general methods:

Example	Product	General methods	TLC
450	(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}-azetidin-3-yl)dimethylamine, oxalate	165C, 249, 423B	0.22(A)
452	1-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ol, oxalate	423B	0.18(D)
461	2-[(1-methylpiperidin-4-yloxy)[3-(pyrrolidin-3-yloxy)phenyl]methyl]-1H-benzimidazole, dioxalate	272A, 272B, 258	0.04(D)
496	2-[(5-chloro-2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate	272A, 272B	0.14(B)

498	2-[(2-fluoro-5-trifluoromethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate	272A, 272B	0.25(A)
503	6-{3-[(1-ethyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine,oxalate	194, 189, 472	0.08(E)
504	2-[(2-fluoro-5-methoxyphenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]-1H-benzimidazole, oxalate	165C, 449A	0.33(E)
517	2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethylsulfanylphenyl)methyl]-1H-benzimidazole, oxalate	272A, 272B	0.36(A)
518	2-[(4-fluoro-3-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate	272A, 272B	0.32(A)
519	2-[(2-fluoro-5-propoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate	272A, 272B	0.33(A)
597	4-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol	578	0.20(A)

Eluent A: CH₂Cl₂/MeOH/NH₄OH 90/10/0.5

Eluent B: CH₂Cl₂/MeOH/NH₄OH 95/5/0.5

Eluent C: CH₂Cl₂/MeOH 90/10

Eluent D: CH₂Cl₂/MeOH/NH₄OH 90/10/1

Eluent E: CH₂Cl₂/MeOH/NH₄OH 80/20/0.5

5

Further examples can be prepared according to the described general methods:

Example	Product	General methods
491	2-[[3-(3,3-difluoropyrrolidin-1-yl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, dioxalate	272A, 272B
¹ H NMR of the base (CDCl ₃): 9.90 (sl, 1H), 7.69 (sl, 1H), 7.18 (m, 3H), 6.86 (d, 1H), 6.64 (s, 1H), 6.43 (d, 1H), 5.80 (s, 1H), 3.65-3.35 (m, 5H), 2.67 (m, 2H), 2.38 (m, 3H), 2.22 (s, 3H), 2.20-1.60 (m, 5H)		

Example	Product	General methods
492	2-[[3-(5-fluorohexahydrocyclopenta[c]pyrrol-2-yl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, dioxalate	423B
¹ H NMR of the base (CDCl ₃): 7.96 (d, 1H), 7.85 (d, 1H), 7.15-7.50 (m, 3H), 6.90 (d, 1H), 6.80 (s, 1H), 6.57 (d, 1H), 5.85 (s, 1H), 5.25 (d, 1H), 3.66 (m, 1H), 3.33 (m, 2H), 3.17 (m, 2H), 3.00 (m, 2H), 2.73 (m, 2H), 2.30 (s, 3H), 2.40-1.60 (m, 10H).		
451	6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexylamine, oxalate	432, 150
¹ H NMR (base): 7.65-7.48 (m, 2H), 7.43 (s, 1H), 7.30-7.15 (m, 5H), 5.85 (s, 1H), 3.60-3.45 (m, 1H), 2.86 (t, 2H, <i>J</i> = 7.1Hz), 2.78-2.60 (m, 4H), 2.23 (s, 3H), 2.18-1.50 (m, 10H), 1.50-1.20 (m, 2H).		
457	5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}oxazolidin-2-one	359B
mp = 109°C		
458	N-(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexyl)guanidine, dihydrochloride	278,432, 150
¹ H NMR (dmso-d ₆): 7.65-7.48 (m, 2H), 7.43 (s, 1H), 7.30-7.15 (m, 5H), 5.85 (s, 1H), 3.60-3.45 (m, 1H), 2.86 (t, 2H, <i>J</i> = 7.1Hz), 2.78-2.60 (m, 4H), 2.23 (m, 3H), 2.18-1.50 (m, 10H), 1.50-1.20 (m, 2H).		
473	4-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}but-2-enylamine	437B, 359B,
MS, [M+H] ⁺ = 423.2		
474	4-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}but-2-enylamine, oxalate	437B, 359B,
478	N-(2-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-N-isobutyrylguanidine	401
MS, [M+H] ⁺ = 509.2 ; [M+Na] ⁺ = 531.1		
488	3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}allylamine	437B, 53
mp = 183°C ; MS, [M+H] ⁺ = 377.3 ; [M+Na] ⁺ = 399.1		
494	cis-2-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}cyclopropylmethylamine	437B, 359B
mp = 99°C ; MS, [M+H] ⁺ = 437.1 ; [M+Na] ⁺ = 459.2		

499	N-(3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}allyl)guanidine, trihydrochloride	278 , 437B, 359B
MS, $[M+H]^+ = 419.2$; $[M+Na]^+ = 441.3$		
502	2-[(azetidin-3-ylmethoxy)(3-bromophenyl)methyl]-1H-benzimidazole	210, 165D, E
mp = 104 °C		
506	2-[(3-bromophenyl)(1-methylazetidin-3-ylmethoxy)methyl]-1H-benzimidazole	165C, 437B, 210, 165D, E
MS, ^{79}Br $[M+H]^+ = 386.1$; $[M+Na]^+ = 408.0$; MS, ^{80}Br $[M+H]^+ = 388.0$; $[M+Na]^+ = 410.0$		
512	2-[(2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 1B
mp = 210 °C		
513	2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 1B
mp = 85 °C		
514	2-[(5-ethylsulfanyl-2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	150, 272A, 1B
mp = 90 °C		
515	2-[(azetidin-3-ylmethoxy)(2-fluoro-5-trifluoromethoxyphenyl)methyl]-1H-benzimidazole, oxalate	165B, A, D, E
^1H NMR (base) : 7.57-7.62 (m, 2H), 7.38-7.52 (m, 1H), 7.25-7.11 (m, 4H), 6.07 (s, 1H), 3.99-3.90 (m, 2H), 3.80-3.74 (m, 2H), 3.64-3.51 (m, 2H), 2.88-3.00 (m, 1H).		
516	2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylazetidin-3-ylmethoxy)methyl]-1H-benzimidazole, oxalate	165C, B, A, D, E
^1H NMR (base) : 7.65-7.48 (m, 2H), 7.38-7.33 (m, 1H), 7.25-7.10 (m, 4H), 6.04 (s, 1H), 3.89-3.70 (m, 2H), 3.44-3.48 (m, 1H), 3.32-3.38 (m, 3H), 2.52-2.76 (m, 1H), 2.44 (m, 3H)		
520	2-[(3-ethylsulfanyl-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	150, 272A, 1B
mp = 150 °C		
521	2-[(2,2-difluorobenzo[1,3]dioxol-5-yl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole	272A, 1B
MS, $[M+H]^+ = 402.1$		
538	2-[(piperidin-4-yloxy)thiophen-3-ylmethyl]-1H-benzimidazole	165B, A, D, E

¹ H NMR: 9.50 (sl, 1H), 7.75 (sl, 1H), 7.48 (sl, 1H), 7.38-7.22 (m, 5H), 7.12-7.05 (m, 1H), 5.98 (s, 1H), 3.75-3.60 (m, 1H), 3.20-3.05 (m, 2H), 2.72-2.55 (m, 2H), 2.10-1.85 (m, 2H), 1.70-1.45 (m, 2H)		
539	2-[(1-methylpiperidin-4-yloxy)thiophen-3-ylmethyl]-1H-benzimidazole	165C, B, A, D, E
MS, [M+H] ⁺ = 328.03		
544	2-[(piperidin-4-yloxy)thiophen-2-ylmethyl]-1H-benzimidazole	165B, A, D, E
mp = 185 °C		
546	2-[(1-methylpiperidin-4-yloxy)thiophen-2-ylmethyl]-1H-benzimidazole	165C, B, A, D, E
mp = 85 °C		

Preparation of starting materials

5 Salicaldehydes can be prepared from the corresponding phenols according to following procedures (non exhaustive):

-with paraformaldehyde, magnesium chloride and triethylamine according *J. Med. Chem.*, 2006, 49 (26), pp 7731–7739.

10 -protection of phenol with a tetrahydropyranyl (THP) group followed by metalation and addition of dimethylformamide and final THP deprotection according to WO2009/089057

-with the Reimer-Tiemann procedure *Org. React.* **1982**, 28, 2)

-with hexamethylenetetramine (Duff reaction, *Organic Syntheses Coll.* Vol. 10, p.96; Vol. 75, p.1)

15

Biological data

In vitro evaluation of compounds

- Membrane preparation

20 SH-SY5Y cells stably expressing human H4 receptor are grown until sub-confluence and centrifuged at 300g 15 minutes at 4 °C. Pellets are resuspended in buffer I Tris-HCl 50mM, MgCl₂ 10mM, NaCl 140mM, pH=7.4 supplemented by Leupeptin 10µg/mL, Phenyl Methyl Sulphonyl Fluoride (PMSF) 0.1mM, Aprotinin 2µg/mL and Pepstatin 2µM (or a 1/50 dilution of a mix of protease inhibitors). The obtained suspension

25 is stirred gently and submitted to a 25-26xg mechanic pressure exerted through a syringe.

The cell lysate is then centrifuged at 300g 15 minutes at 4°C in order to eliminate nucleus and cell scraps. The obtained supernatant is then centrifuged at 48000 g for 30 minutes at 4°C. The final pellet is resuspended in buffer I with a potter homogenizer. Aliquots are frozen in liquid nitrogen and stored until use at -80°C. Protein content is measured by the
5 Bradford method.

- GTPγ [³⁵S] binding

Defreezed membranes are diluted at a final concentration of 5μg/180μL/well in buffer I supplemented by GDP 10μM and distributed in 96 well polystyrene microplate.
10 GTPγ [³⁵S] labelled ligand (0.2-0.3 nM) is added for additional 30 minutes. After transfer in a Millipore GF/C HTS[®] microplate, the filtration of the reactional mix is followed by a three times 250 μl wash to stop the reaction.

The filter-bound radioactivity is measured in a liquid scintillation counter Microbeta TRILUX[®] with 50μl of scintillation fluid.

15 GTPγ [³⁵S] dependent binding activity is determined in vitro for Histamine, Imetit, R(-)-alpha-methyl-histamine and all our compounds.

Compounds can also be tested against Histamine or Imetit to evaluate their antagonist potential. Results are expressed with IC50 and Ki values.

20

- Membrane preparation

CHO cells stably expressing human H4 receptor were grown until sub-confluence and centrifuged at 300g 15 minutes at 4°C. Pellets were resuspended in buffer I Tris-HCl 50mM, MgCl₂ 10mM, NaCl 140mM, pH=7,4 supplemented by a 1/50 dilution of a mix of protease inhibitors. The obtained suspension is stirred gently and submitted to a 25-26xg
25 mechanic pressure exerted through a syringe. The cell lysate is then centrifuged at 300g 15 minutes at 4°C in order to eliminate nucleus and cell scraps. The obtained supernatant was then centrifuged at 48000 g for 30 minutes at 4°C. The final pellet is resuspended in buffer I with a potter homogenizer. Aliquots were frozen in liquid nitrogen and stored until use at -80°C. Protein content is measured by the Bradford method.

30

- [³H]Histamine binding

Defreezed membranes were diluted at a final concentration of 20μg / 180μL/ well in a binding buffer containing 50 mM Tris/HCl, 0.5 mM EDTA, pH=7.4 and distributed in 96 well polystyrene microplate. [³H] Histamine labelled ligand (10-15 nM) is added for 60
35 minutes with compounds at room temperature under continuous stirring. Non specific binding was estimated in the presence of 10 μM BP1.2404 (JNJ 7777120). The reaction

was terminated by filtration through GF/B filters pre-soaked 2 hours at 4 °C in 1 % polyethyleneimine. Filters were rinsed 3 times with 250 µl of ice cold incubation binding buffer.

The filter-bound radioactivity was measured in a liquid scintillation counter
5 Microbeta TRILUX® with 50µl of scintillation fluid.

The hH4 binding investigated by use of [³H] Histamine give a Bmax ~1 pmole/mg prot and a Kd ~9 nM.

Racemates described hereabove have been evaluated in the GTPγ [³⁵S] assay or in
10 the [³H] histamine binding assay and have been found active with a Ki or IC50 under 1000nM.

Example	Activity
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1	B
2	A
3	B
4	A
5	B
6	B
7	B
8	C
9	C
10	C
11	C
12	B
13	B
14	A
15	B
16	C
17	A
18	B
19	B
20	B
21	B
22	C
23	C
24	A
25	C
26	C
27	C
28	B
29	A
30	B
31	C
32	B
33	B
34	B
35	A

Example	Activity
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36	B
37	A
38	B
39	B
40	C
41	C
42	C
43	B
44	A
45	C
46	B
47	C
48	B
49	A
50	C
51	C
52	A
53	B
54	B
55	C
56	B
57	C
58	B
59	C
60	C
61	C
62	C
63	B
64	A
65	C
66	A
67	C
68	B
69	C
70	B

Example	Activity
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71	B
73	B
74	B
75	C
76	B
77	B
78	B
79	B
80	B
81	B
82	B
83	B
84	A
85	B
86	B
87	B
88	C
89	B
90	B
91	C
92	B
93	B
94	C
95	C
96	B
97	B
98	B
99	B
100	B
101	C
102	C
103	B
104	C
105	C
106	B

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Example	Activity
107	C
108	B
109	B
110	B
111	C
112	A
113	C
114	B
115	B
116	B
117	C
118	C
119	B
120	A
121	B
122	B
123	A
124	C
125	C
126	B
127	B
128	B
129	C
130	B
131	B
132	B
133	B
134	B
135	B
136	B
137	B
138	B
139	C
140	B
141	B
142	B
143	B
144	C
145	B
146	B
147	B
148	B
149	C
150	B
151	B
152	C
153	C
154	B
155	B
156	C
157	B
158	C
159	C

Example	Activity
160	C
161	C
162	C
163	C
164	B
165	B
166	C
167	C
168	B
169	A
170	B
171	C
172	B
173	B
174	B
175	B
176	C
177	B
178	B
179	B
180	C
181	C
182	C
183	B
184	B
185	C
186	A
187	C
188	C
189	B
190	B
191	B
192	B
193	B
194	B
195	B
196	C
197	C
198	C
199	B
200	B
201	C
202	C
203	A
204	B
205	A
206	B
207	A
208	B
209	B
210	A
211	B
212	A

Example	Activity
213	B
214	B
215	B
216	B
217	B
218	C
219	A
220	C
221	B
222	B
223	B
224	B
225	B
226	B
227	C
228	C
229	C
231	B
232	A
233	B
234	B
235	A
236	B
237	B
238	A
239	A
240	B
241	B
242	A
243	B
244	B
245	B
246	B
247	B
248	B
249	B
250	B
251	A
252	A
253	C
254	C
255	C
256	C
257	A
258	B
259	B
260	C
261	B
262	B
263	A
264	B
265	B
266	B

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Example	Activity
267	C
268	B
269	C
270	A
271	C
272	A
273	A
274	B
275	B
276	C
277	B
278	C
279	A
280	B
281	A
282	A
283	C
284	B
285	A
286	B
287	C
288	A
289	C
290	B
291	B
292	B
293	B
294	C
295	B
296	B
297	B
298	A
299	A
300	B
301	C
302	C
303	B
304	C
305	C
306	B
307	A
308	B
309	B
310	B
311	B
312	B
313	B
314	C
315	A
316	B
317	A
318	C
319	C

Example	Activity
320	C
321	C
322	A
323	A
324	B
325	C
326	C
327	B
328	C
330	B
331	B
332	A
333	B
334	B
335	B
336	B
337	C
338	B
339	B
340	C
341	B
342	B
343	B
344	B
345	B
346	B
347	A
348	A
349	B
350	A
351	A
352	B
353	B
354	C
355	B
356	A
357	B
358	C
359	C
360	A
361	A
362	A
363	B
364	A
365	B
366	C
367	B
368	C
369	A
370	A
371	C
372	C
373	C

Example	Activity
374	C
375	A
376	A
377	B
378	A
379	A
380	B
381	C
382	C
383	B
384	B
385	B
386	C
387	C
388	A
389	B
390	C
391	A
392	A
393	C
394	A
395	B
396	A
397	B
398	B
399	B
400	C
401	B
402	B
403	B
404	B
405	B
406	C
407	C
408	B
409	B
410	B
411	A
412	A
413	B
414	B
415	B
416	B
417	A
418	C
419	A
421	C
422	C
423	B
424	B
425	C
426	B
427	B

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Example	Activity
428	B
429	B
430	C
431	C
433	C
435	C
436	C
437	C
438	C
439	C
440	C
441	C
442	C
443	C
444	B
445	B
446	B
447	A
448	B
449	C
450	A
451	B
452	B
453	C
454	C
455	C
456	A
457	C
458	B
459	C
460	A
461	B
462	B
463	A
464	C
465	C
466	C
467	C
468	B
469	A
470	B
471	B
472	B
473	C
474	C
475	B
476	C
477	A
478	B
479	C
480	B
481	A
482	C

Example	Activity
483	B
484	C
485	A
486	C
487	C
488	A
489	C
490	B
491	A
492	A
493	C
494	C
495	C
496	B
497	A
498	B
499	C
500	B
501	B
502	A
503	B
504	C
505	A
506	B
507	C
508	C
509	C
510	B
511	B
512	C
513	C
514	C
515	A
516	B
517	C
518	A
519	C
520	B
521	A
522	C
523	C
524	B
525	B
526	C
527	C
528	B
529	B
530	A
531	C
532	B
533	C
534	B
535	B

Example	Activity
536	C
537	A
538	A
539	B
540	B
541	C
542	C
543	C
544	A
545	B
546	B
547	A
548	C
549	A
550	C
551	B
552	B
553	A
554	B
555	C
556	C
557	C
558	C
559	C
560	B
561	C
562	C
563	B
564	C
565	B
566	C
567	B
568	C
569	C
570	B
571	C
572	C
573	B
574	C
575	C
576	C
577	B
578	C
579	A
580	A
581	C
582	C
583	B
584	C
585	C
586	C
587	C
588	C

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Example	Activity
589	A
590	A
591	B
592	B
593	C
594	C
595	B
596	C
597	A
598	B
599	B
600	C
601	C

Example	Activity
602	B
603	B
604	B
605	C
606	B
607	A
608	B
609	B
610	A
611	C
612	C
613	C
614	C

Example	Activity
615	B
616	C
617	C
618	C
619	B
620	C
621	C
622	B
623	C
624	C
625	C
627	C

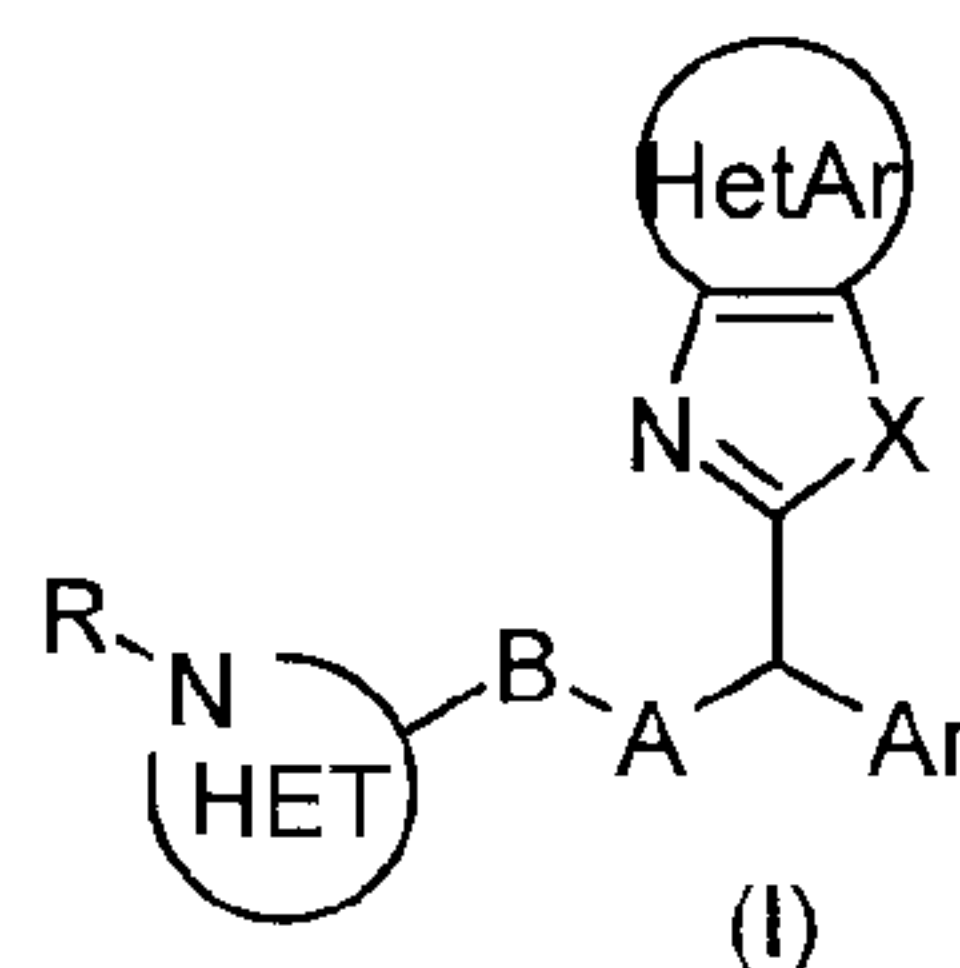
A: Ki or IC50 <1000nM

B: Ki or IC50 <300nM

C: Ki or IC50 <30nM

CLAIMS

1. A compound of formula (I):



5 wherein:

X represents NR', S or O;

HetAr represents a phenyl or heteroaryl, optionally substituted with one or more substituents chosen from halogen, OR'', alkyl, cyano, NR''R''', -COR'', -COOR'', -CONR''R''', aryl, -alkylaryl;

10 R represents a lower alkyl or H

R' represents H, lower alkyl, alkoxyalkyl or alkoxycarbonyl;

R'', R''' identical or different independently represent H or alkyl;

HET representing a non aromatic monocyclic heterocycle containing at least one nitrogen atom, which is linked to R;

15 B represents a single bond or an -alkyl- group;

A represents O, NH or S;

Ar is a mono or polycyclic aromatic or a mono or polycyclic heteroaromatic which can be optionally substituted with one or more of:

- halo; azido; cyano; hydroxy; nitro;
- 20 • alkyl; alkoxy; alkylsulfanyl; alkenyl; alkynyl; alkenyloxy; alkenyloxy; alkenylsulfanyl; alkynylsulfanyl; cycloalkoxy; cyloalkylalkyl;

whose alkyl, alkenyl, alkynyl or cycloalkyl part can be substituted with one or more of halo, hydroxy, polyhydroxy, alkoxy, hydroxyalkoxy, cyano, amino, aminoalkyl, alkylamino, dialkylamino, aminoalkylamino, aminoalkylaminocarbonyl, alkoxycarbonylamino, diarylmethylimino (where aryl is optionally substituted with one or more of hydroxy or halo), cycloalkenylimino (where cylalkenyl is optionally substituted with one or more of alkyl, OH), alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, cycloalkyl, polycycloalkyl, cycloalkenyl, polycycloalkenyl, guanidino,

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alkylcarbonylguanidino, acylguanidino, cyanoguanidino, alkoxy carbonylguanidino, alkoxy carbonyl, alkoxy carbonylalkylamino, alkoxy carbonylalkylcycloalkyl, alkoxy carbonylheterocyclyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylalkoxy, aryloxy, arylsulfanyl, arylsulfinyl, arylsulfonyl, heteroaryl, heterocyclyl (heterocyclyl being optionally substituted with one or more of oxo, amino, imino), heteroaryloxy, heterocyclyloxy, heteroaryl amino, heterocyclyl amino, hydrazinocarbonyl, hydroxyalkylcycloalkyl, N-alkyl(thioureido), phthalimido, ureido, oxocycloalkenyl amino substituted with amino, carbamimidoylheterocyclyl;

- amino; alkylamino; alkylcarbonyl; alkoxy carbonyl; alkylsulfanyl; alkylsulfinyl; alkylsulfonyl; alkylsulfonyloxy
- whose alkyl can be substituted with one or more of halo;
- aminocarbonyl which can be N-substituted with one or two of alkyl, aryl, arylalkyl;
 - aryl; arylalkyl; aryloxy; arylalkoxy; arylalkyl amino; arylalkylsulfanyl; heteroaryl; heteroaryloxy

whose aryl part can be substituted with one or more of amino, halo, alkyl, (poly)haloalkyl, hydroxyalkyl, alkoxy, (poly)haloalkoxy, alkoxy carbonyl amino, alkylcarbonyl, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, nitro, cyanoalkyl, or fused with a non aromatic heterocycle;

- heterocyclyl; heterocyclyloxy; heterocyclylalkoxy
- whose heterocycle can be substituted with one or more of halogenoalkyl, acyl amino, acyloxy, amino, alkyl, alkyl amino, dialkyl amino, aminoalkyl, oxo, carbamimidoyl, halo, hydroxy, hydroxyalkyl, hydroxymethyl, alkoxy carbonyl;

- fused with a non aromatic heterocycle (optionally substituted with one or more of halogens) or carbocycle;

as well as their enantiomers, diastereomers, mixtures thereof and pharmaceutically acceptable salts, tautomers, hydrates and solvates.

2. The compound according to claim 1 wherein:

wherein:

X represents NR' or S;

HetAr represents a phenyl, optionally substituted with one or more substituents chosen from hydrogen, halogen, amino, alkyl;

R represents H or a lower alkyl;

R' represents H, alkyl, alkoxyalkyl, alkoxycarbonyl;

5 HET representing a non aromatic 5 or 6 membered heterocycle containing one nitrogen atom, which is linked to R;

B represents a single bond or a $-CH_2-$ group;

A represents O, NH or S;

10 Ar is a thienyl, phenyl or naphthyl or 5 to 6 membered heteroaromatic where the phenyl can be optionally substituted with one or more of:

- halo; azido; cyano; hydroxy; nitro; alkyl;
- alkoxy; alkylsulfanyl; alkenyl; alkenylsulfanyl; alkynyl; alkenyloxy; alkenyloxy; cycloalkoxy; cycloalkylalkyl

15 whose alkyl, alkenyl, alkynyl or or cycloalkyl part can be substituted with one or more of halo, hydroxy, alkoxy, hydroxyalkoxy, cyano, amino, aminoalkyl, alkylamino, aminoalkylamino, dialkylamino, aminoalkylaminocarbonyl, alkoxycarbonylamino, diarylmethylimino (where aryl is optionally substituted with one or more of hydroxy or halo), cycloalkenylimino (where cylalkenyl is optionally substituted with one or more of alkyl, OH), alkylsulfanyl, alkylsulfonyl, cycloalkyl, (poly)cycloalkenyl, guanidino, 20 alkylcarbonylguanidino, acylguanidino, alkoxycarbonylguanidino, alkoxycarbonyl, alkoxycarbonylalkylamino, alkoxycarbonylheterocyclyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylalkoxy, aryloxy, arylsulfonyl, heteroaryl, heterocyclyl (heterocyclyl being optionally substituted with one or more of oxo, amino, imino), heterocyclylamino, hydrazinocarbonyl, N-alkyl(thioureido), 25 phtalimido, ureido, oxocycloalkenylamino substituted with amino, carbamimidoylheterocyclyl;

- amino; alkylamino; alkylcarbonyl; alkoxycarbonyl; alkylsulfanyl; alkylsulfonyl; alkylsulfonyloxy

whose alkyl can be substituted with one or more of halo;

- 30
- aminocarbonyl which can be N-substituted with one or two of alkyl, aryl, arylalkyl;
 - aryl; arylalkyl; aryloxy; arylalkoxy; arylalkylsulfanyl; heteroaryl; heteroaryloxy

whose aryl part can be substituted with one or more of amino, halo, alkyl, (poly)haloalkyl, hydroxyalkyl, alkoxy, (poly)haloalkoxy, alkoxycarbonylamino, alkylcarbonyl, alkylsulfanyl, nitro, cyanoalkyl, or is fused with a non aromatic heterocycle;

- 5 • heterocycloxy; heterocyclylalkoxy; heterocyclyl

whose heterocycle can be substituted with one or more of halo, halogenoalkyl, acylamino, acyloxy, amino, alkyl, alkylamino, dialkylamino, aminoalkyl, oxo, carbamimidoyl, hydroxy, hydroxyalkyl;
or

- 10 • fused with a non aromatic heterocycle (optionally substituted with one or more of halogens) or carbocycle;

as well as their enantiomers, diastereomers, mixtures thereof and pharmaceutically acceptable salts, tautomers, hydrates and solvates.

- 15 3. The compound of formula (I) according to claim 1 or 2, where X represents NH or S.

4. The compound according to any one of claims 1-3, wherein HetAr is phenyl.

5. The compound according to any one of claims 1-4, wherein R represents methyl.

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6. The compound according to any one of claims 1-5, wherein B represents a single bond.

- 25 7. The compound according to any one of claims 1-6, wherein Ar is a phenyl which can be optionally substituted with one or more of:

halo; azido; cyano; hydroxy; nitro; alkyl;
alkoxy; alkylsulfanyl; alkenyl; alkynyl; alkenyloxy; alkenyloxy;

- 30 whose alkyl; alkenyl or alkynyl part can be substituted with one or more of halo, hydroxy, alkoxy, hydroxyalkoxy, cyano, amino, alkylamino, aminoalkylamino, alkylsulfanyl, alkylsulfonyl, cycloalkyl, (poly)cycloalkenyl, guanidino, acylguanidino, alkoxycarbonylguanidino, alkoxycarbonyl, alkoxycarbonylalkylamino, alkoxycarbonylheterocyclyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl,

alkylcarbonylalkoxy, aryloxy, arylsulfonyl, heteroaryl, heterocyclyl, heterocyclylamino, hydrazinocarbonyl, N-alkyl(thioureido), phthalimido, ureido, oxocycloalkenylamino substituted with amino, carbamimidoylheterocyclyl;

amino; alkylamino; alkylcarbonyl; alkoxy carbonyl; alkylsulfanyl; alkylsulfonyl;

5 alkylsulfonyloxy

whose alkyl can be substituted with one or more of halo;

aminocarbonyl which can be N-substituted with one or two of alkyl, aryl, arylalkyl;

aryl; aryloxy; arylalkoxy; arylalkylsulfanyl; heteroaryl

10 whose aryl part can be substituted with one or more of amino, halo, alkyl, (poly)haloalkyl, hydroxyalkyl, alkoxy, (poly)haloalkoxy, alkoxy carbonylamino, alkylcarbonyl, alkylsulfanyl, nitro, cyanoalkyl, or is fused with a non aromatic heterocycle;

heterocycliloxy; heterocyclylalkoxy

15 whose heterocycle can be substituted with one or more of acylamino, acyloxy, amino, alkyl, carbamimidoyl, hydroxy, hydroxyalkyl;

or

fused with a non aromatic heterocycle.

20 8. The compound according to any one of claims 1-7 which is chosen from the group consisting in:

- 2-[(1-methylpiperidin-4-yloxy)phenylmethyl]benzothiazole
- 2-[(1-methylpyrrolidin-3-yloxy)phenylmethyl]benzothiazole
- 2-[(4-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(4-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 25 - 2-[(3-fluorophenyl)(1-methylpiperidin-4-yloxymethyl]benzothiazole
- 2-[(2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)-p-tolylmethyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(m-tolyl)methyl]benzothiazole
- (benzothiazol-2-yl-phenylmethyl)(1-methylpiperidin-4-yl)amine
- 30 - 2-[(2,3-dihydrobenzo[1,4]dioxin-6-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(2,4-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole

- 2-[(1-methylpiperidin-4-yloxy)thiophen-2-ylmethyl]benzothiazole
- 2-[(4-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3,5-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)thiophen-3-ylmethyl]benzothiazole
- 5 - 2-[(1-methylpiperidin-4-yloxy)naphthalen-1-ylmethyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)naphthalen-2-ylmethyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(5-methylthiophen-2-yl)methyl]benzothiazole
- 2-[benzo[1,3]dioxol-5-yl(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [(benzothiazol-2-yl)(m-tolyl)methyl](1-methylpiperidin-4-yl)amine
- 10 - 2-[(3-allyloxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethoxyphenyl)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(4-trifluoromethoxyphenyl)methyl]benzothiazole
- [benzothiazol-2-yl(3-methoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(1-methylpiperidin-4-yloxy)(3-propoxy-phenyl)methyl]benzothiazole
- 15 - 2-[(3-bromo-phenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(3-phenoxy-phenyl)methyl]benzothiazole
- 5-methyl-2-[(1-methylpiperidin-4-yloxy)phenylmethyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)phenylmethyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethylphenyl)methyl]benzothiazole
- 20 - 2-[(2,3-dihydrobenzofuran-5-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 5-fluoro-2-[(1-methylpiperidin-4-yloxy)phenylmethyl]benzothiazole
- 2-[(4-fluoro-3-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [benzothiazol-2-yl(4-fluoro-3-methyl-phenyl)methyl](1-methylpiperidin-4-yl)amine
- (benzothiazol-2-yl-p-tolylmethyl)(1-methylpiperidin-4-yl)amine
- 25 - [(benzofuran-2-yl)(benzothiazol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(3-fluoro-5-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [(1*H*-benzimidazol-2-yl)phenylmethyl](1-methylpiperidin-4-yl)amine
- 2-[(3-fluoro-5-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 30 - [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [benzothiazol-2-yl(3-fluoro-5-methoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [benzothiazol-2-yl(3-fluoro-5-methylphenyl)methyl](1-methylpiperidin-4-yl)amine

- 2-[(3-benzyloxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[benzofuran-5-yl(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-ethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [benzothiazol-2-yl(3-iodophenyl)methyl](1-methylpiperidin-4-yl)amine
- 5 - 2-[(1-methylpiperidin-4-yloxy)(3-propoxyphenyl)methyl]-1*H*-benzimidazole
- [(1*H*-benzimidazol-2-yl)(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- (benzothiazol-2-ylpyridin-3-ylmethyl)(1-methylpiperidin-4-yl)amine
- 2-[biphenyl-3-yl(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 10 - {3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxymethyl)biphenyl-3-yl}methanol
- 2-[(3-isopropoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [benzothiazol-2-yl(3-propoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [benzothiazol-2-yl(1*H*-pyrrol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- 15 - [(1*H*-benzimidazol-2-yl)(3-trifluoromethylphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-trifluoromethoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-ethylphenyl)methyl](1-methylpiperidin-4-yl)amine
- 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenol
- 2-[(1-methylpiperidin-4-yloxy)(3-pyridin-3-ylphenyl)methyl]benzothiazole
- 20 - [(1*H*-benzimidazol-2-yl)(3-bromophenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-benzyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-isopropylphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-isobutoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(3-methylbutoxy)phenyl]methyl}(1-methylpiperidin-4-
- 25 yl)amine
- [(1*H*-benzimidazol-2-yl)(3-butoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-methoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- trifluoromethanesulfonic acid 3-[benzothiazol-2-yl(1-methylpiperidin-4-
- yl)oxy)methyl]phenyl ester
- 30 - trifluoromethanesulfonic acid 3-[benzothiazol-2-yl(1-methylpiperidin-4-
- yl)oxy)methyl]phenyl ester

- [(1*H*-benzimidazol-2-yl)(3-cyclohexylmethoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-fluorophenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-methylsulfanylphenyl)methyl](1-methylpiperidin-4-yl)amine
- 5 - [(1*H*-benzimidazol-2-yl)(3-hexylphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-isopropoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-ylamine
- 2-[(3-butylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 10 - 2-[biphenyl-3-yl(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- [benzothiazol-2-yl(3-bromophenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-ethoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(*m*-tolyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-phenoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 15 - {3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-yl}methanol
- 3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-ylamine
- [benzothiazol-2-yl(3-isopropoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(1-methylpiperidin-4-yloxy)(3-pyridin-3-ylphenyl)methyl]-1*H*-benzimidazole
- 1-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-ylamino)methyl]phenyl}ethanone
- 20 - [benzothiazol-2-yl(3-butoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(3-butoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- [benzothiazol-2-yl(3-cyclohexylmethoxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)biphenyl-3-ylmethyl](1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-pentyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 25 - 2-[(2'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(3'-nitrobiphenyl-3-yl)methyl]benzothiazole
- {3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-yl}acetonitrile
- 2-[(3'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(4'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 30 - [benzothiazol-2-yl(3-benzyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- (benzothiazol-2-ylbiphenyl-3-ylmethyl)(1-methylpiperidin-4-yl)amine

- {(1*H*-benzimidazol-2-yl)[3-(4-fluorobenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-benzylsulfanylphenyl)methyl](1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(3-fluorobenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 5 - {(1*H*-benzimidazol-2-yl)[3-(2-phenoxyethoxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- [benzothiazol-2-yl(3-benzylsulfanylphenyl)methyl](1-methylpiperidin-4-yl)amine
- 1-{3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-yl}ethanone
- 10 - 2-[(3'-fluoro-biphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 1-{3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-3-yl}ethanone
- [benzothiazol-2-yl(3-methylsulfanylphenyl)methyl](1-methylpiperidin-4-yl)amine
- [(3-allyloxyphenyl)(1*H*-benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(2-fluorobenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 15 - 2-[(1-methylpiperidin-4-yloxy)(2'-methylsulfanylbiphenyl-3-yl)methyl]-1*H*-benzimidazole
- 2-[(4'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)(3'-methylsulfanylbiphenyl-3-yl)methyl]-1*H*-benzimidazole
- 20 - 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(4'-trifluoromethylbiphenyl-3-yl)methyl]-1*H*-benzimidazole
- {(1*H*-benzimidazol-2-yl)[3-(tetrahydropyran-2-yloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 25 - 2-[(2'-chlorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(3',4'-dichlorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- {3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-2-yl}methanol
- {(1*H*-benzimidazol-2-yl)[3-(4-methoxybenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 30 - {(1*H*-benzimidazol-2-yl)[3-(3-methoxybenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine

- 3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-ylamino)methyl]phenol
- {3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-2-yl}methanol
- 2-[(1-methylpiperidin-4-yloxy)(3'-methylsulfanyl)biphenyl-3-yl)methyl]benzothiazole
- {(1*H*-benzimidazol-2-yl)[3-(2-methylbenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 5 - {(1*H*-benzimidazol-2-yl)[3-(4-methylbenzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-nitrophenyl)methyl](1-methylpiperidin-4-yl)amine
- [(3-azidophenyl)(1*H*-benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- 10 - 2-[(3',4'-dichlorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- {(1*H*-benzimidazol-2-yl)[3-(2-ethoxyethoxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- [(1*H*-benzimidazol-2-yl)(3-pent-4-enyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- 2-[(4'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 15 - 2-[(2'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- {3'-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-yl}carbamic acid *tert*-butyl ester
- 2-[(3'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(4'-trifluoromethylbiphenyl-3-yl)methyl]benzothiazole
- 20 - 2-[(1-methylpiperidin-4-yloxy)(2',3',4'-trifluorobiphenyl-3-yl)methyl]benzothiazole
- 2-[(2'-fluorobiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- {3'-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-yl}carbamic acid *tert*-butyl ester
- [(1*H*-benzimidazol-2-yl)(3-furan-2-ylphenyl)methyl](1-methylpiperidin-4-yl)amine
- 25 - [(1*H*-benzimidazol-2-yl)(3-but-3-enyloxyphenyl)methyl](1-methylpiperidin-4-yl)amine
- {(1*H*-benzimidazol-2-yl)[3-(4-methylpentyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 2-[(1-methylpiperidin-4-yloxy)(3-pyrazol-1-ylphenyl)methyl]benzothiazole
- 2-[(3-benzylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 30 - {(1*H*-benzimidazol-2-yl)[3-(2,5-difluoro-benzyloxy)phenyl]methyl}(1-methylpiperidin-4-yl)amine
- 2-[(3-benzylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

- 2-[(2-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(3-ethylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(3-ethylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- {3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid
- 5 methyl ester
- 2-[(3-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[[3-(2,5-difluorobenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
- 10 - 2-[(3-ethylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid
- methyl ester
- 2-[[3-(2,3-difluorobenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- {(1*H*-benzimidazol-2-yl)[3-(2,3-difluoro-benzyloxy)phenyl]methyl}(1-methylpiperidin-4-
- 15 yl)amine
- 2-[[3-(2-fluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(*m*-tolyl)methyl]-1*H*-benzimidazole
- 5,6-dichloro-2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-1*H*-benzimidazole
- 5-fluoro-2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-1*H*-benzimidazole
- 20 - 2-[(2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)(3-pent-4-enyloxy-phenyl)methyl]benzothiazole
- 2-{(1-methylpiperidin-4-yloxy)[3-(4,4,4-trifluoro-butoxy)phenyl]methyl}benzothiazole
- 5-bromo-2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-1*H*-benzimidazole
- 2-[[3-(3-fluorobenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 25 - 3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzonitrile
- 2-[[3-(furan-2-ylmethylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1*H*-
- benzimidazole
- ((1*H*-benzimidazol-2-yl)-{3-[3-(2-methyl-[1,3]dioxolan-2-yl)-propoxy]phenyl}methyl)(1-
- methylpiperidin-4-yl)amine
- 30 - {(1*H*-benzimidazol-2-yl)[3-(4,4,4-trifluoro-butoxy)phenyl]methyl}(1-methylpiperidin-4-
- yl)amine
- 2-[[3-(3-fluoropropoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole

- 2-[(1-methylpiperidin-4-yloxy)-p-tolyl-methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(3,3,3-trifluoro-propoxy)phenyl]methyl]benzothiazole
- 2-[(4-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- {(1*H*-benzimidazol-2-yl)[3-(2-fluoro-ethoxy)phenyl]methyl}(1-methylpiperidin-4-
- 5 yl)amine
- ((1*H*-benzimidazol-2-yl)-{3-[2-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)ethoxy]phenyl]methyl)(1-methylpiperidin-4-yl)amine
- 2-[(1-methylpiperidin-4-yloxy)(4'-trifluoromethoxy-biphenyl-3-yl)methyl]-1*H*-benzimidazole
- 10 - 2-[(4'-methoxybiphenyl-3-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(3-benzo[1,3]dioxol-5-ylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[[3-(3-methoxybenzyloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentan-2-one
- 2-[(1-methylpiperidin-4-yloxy)[3-(3-trifluoromethyl-
- 15 benzyloxy)phenyl]methyl]benzothiazole
- 4-[benzothiazol-2-yl(3-bromo-phenyl)methoxy]-1,1-dimethylpiperidinium
- 2-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)isoindole-1,3-dione
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-yn-1-ol
- 20 - 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-yn-1-ol
- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-yn-1-ol
- 2-[(1-methylpiperidin-4-yloxy)-o-tolyl-methyl]-1*H*-benzimidazole
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynylamine
- 25 - 2-[(3-ethynylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(3-nitro-benzyloxy)phenyl]methyl]benzothiazole
- 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzonitrile
- 2-[(1-methylpiperidin-4-yloxy)[3-(1*H*-[1,2,3]triazol-4-yl)phenyl]methyl]-1*H*-benzimidazole
- 30 - 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzoic acid methyl ester
- 2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-3*H*-benzimidazol-4-ylamine
- 2-[(1-methylpiperidin-4-yloxy)(3-methylsulfanyl-phenyl)methyl]benzothiazole

- 2-[(1-methylpiperidin-4-yloxy)(3-methylsulfanyl-phenyl)methyl]-1*H*-benzimidazole
- 2-[(3-methanesulfonylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(4-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}acrylic acid *tert*-butyl ester
- 5 - 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzoic acid ethyl ester
- {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}methanol
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}propionic acid *tert*-butyl ester
- 10 - 2-[[3-(2-benzenesulfonylvinyl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)phenyl-methyl]-3*H*-benzimidazol-4-ol
- [benzothiazol-2-yl(4'-methoxy-biphenyl-3-yl)methyl](1-methylpiperidin-4-yl)amine
- 2-[[3-(2-methanesulfonylvinyl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-[(2-chloro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 15 - 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrimidin-2-ol
- 2-[(3-*tert*-butylsulfanylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)(3-pyrimidin-5-yl-phenyl)methyl]benzothiazole
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}acrylonitrile
- 2-[(1-methylpiperidin-4-yloxy)(3-vinyl-phenyl)methyl]benzothiazole
- 20 - 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]-*N*-benzyl-*N*-methylbenzamide
- 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]-*N*-propylbenzamide
- 2-[(2,4-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- [(1*H*-benzimidazol-2-yl)(4'-methoxy-biphenyl-3-yl)methyl](1-methylpiperidin-4-yl)amine
- 3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]-*N*-methyl-*N*-phenylbenzamide
- 25 - 3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylamine
- 2-[(3-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(4-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-yn-1-ol
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy-methyl}-phenylamine
- 30 - 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethanol
- 2-[(3-azidophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole

- 2-((1-methylpiperidin-4-yloxy)[3-(2-pyrazin-2-yl-ethylsulfanyl)phenyl]methyl)-1*H*-benzimidazole
- 2-((1-methylpiperidin-4-yloxy)[3-(2-pyrazin-2-yl-ethylsulfanyl)phenyl]methyl}benzothiazole
- 5 - {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}benzyl-amine
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-3-methyl-butan-1-ol
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-yn-1-ol
- 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-yn-1-ol
- 10 - 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}butan-1-ol
- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-cyclopropyl)acetic acid methyl ester
- 2-((1-methylpiperidin-4-yloxy)[3-(2-[1,2,3]triazol-2-yl-ethylsulfanyl)phenyl]methyl}benzothiazole
- 15 - 2-((1-methylpiperidin-4-yloxy)[3-(2-[1,2,3]triazol-1-yl-ethylsulfanyl)phenyl]methyl}benzothiazole
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-3-methyl-butan-1-ol
- 2-[(1-methylpiperidin-4-yloxy)(3-morpholin-4-yl-phenyl)methyl]benzothiazole
- 20 - 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethanol
- 2-[(1-methylpiperidin-4-yloxy)(3-vinyl-phenyl)methyl]-1*H*-benzimidazole
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-1-ol
- 1-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-2-ol
- 25 - 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol
- 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine
- 30 - 2-((1-methylpiperidin-4-yloxy)[3-(2-methylsulfanyl-ethoxy)phenyl]methyl}benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)(2-trifluoromethoxy-phenyl)methyl]-1*H*-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)-p-tolylmethyl]-1*H*-benzimidazole

- 2-[(1-methylpiperidin-4-yloxy)-p-tolyl-methyl]-1*H*-benzimidazole
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-1-ol
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propan-2-ol
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol
- 5 - 2-(1-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-cyclopropyl)ethanol
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}propan-1-ol
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}-*N*-methylethylacetamide
- 10 - 2-{(1-methylpiperidin-4-yloxy)[3-(2*H*-pyrazol-3-yl)phenyl]methyl}benzothiazole
- 2-[(3-bromo-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(2-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetamide
- {3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetic acid
- 15 hydrazide
- 2-{(1-methylpiperidin-4-yloxy)[3-(pyridin-4-ylmethoxy)phenyl]methyl}benzothiazole
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}butan-1-ol
- 2-[[3-(furan-2-ylmethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 2-(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-cyclopropyl)ethanol
- 20 - 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]benzyloxy}propan-2-one
- 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamine
- 2-[(1-methylpyrrolidin-3-yloxy)phenyl-methyl]-1*H*-benzimidazole
- 25 - [(1*H*-benzimidazol-2-yl)-p-tolyl-methyl](1-methylpiperidin-4-yl)amine
- 2-[(3-ethylsulfanyl-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 1-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyloxy)-propan-2-one
- 30 - 1-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyloxy)-propan-2-ol
- 2-[[3-(2-methoxyethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole

- *N*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine
- (2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)methyl-amine
- 2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethoxy-phenyl)methyl]-1*H*-benzimidazole
- 5 - 2-[(2-chlorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynylamine
- 2-{(1-methylpiperidin-4-yloxy)[3-(pyridin-2-ylmethoxy)phenyl]methyl}benzothiazole
- 2-{(1-methylpiperidin-4-yloxy)[3-(pyridin-3-ylmethoxy)phenyl]methyl}benzothiazole
- 2-[(3-Cyclohexylmethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 10 - 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynylamine
- 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propane-1,2-diol
- 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pentylamine
- 15 - 2-{3-[benzothiazol-2-yl(1-ethyl-piperidin-4-yloxy)methyl]phenoxy}ethylamine
- 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamine
- 6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexan-1-ol
- 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}butylamine
- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-
- 20 - ynylamine
- 6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexan-1-ol
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynylamine
- 2-[benzo[1,3]dioxol-5-yl(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 25 - (2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-urea
- (2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)(4,5-dihydro-thiazol-2-yl)amine
- 2-[(2,3-dihydrobenzo[1,4]dioxin-6-yl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-
- 30 - benzimidazole
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}butylamine

- *N*-(2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propylamine
- *N-tert*-butoxycarbonyl-*N'*-(2-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine
- 5 - 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}pentylamine
- 2-{[3-[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]phenyl}(1-methylpiperidin-4-yloxy)methyl]benzothiazole
- *N-tert*-butoxycarbonyl-*N'*-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine
- 10 - *N*-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}butyl)guanidine
- *N-tert*-butoxycarbonyl-*N'*-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}butyl)guanidine
- 15 - 2-[(1-methylpiperidin-4-yloxy)[3-(pyridin-2-ylmethoxy)phenyl]methyl]-1*H*-benzimidazole
- 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}propylamine
- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pentylamine
- *N-tert*-butoxycarbonyl-*N'*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propyl)guanidine
- 20 - 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propylamine
- 2-[(1-methylpiperidin-4-yloxy)[3-(4-[1,2,3]triazol-2-yl-butoxy)phenyl]methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(4-[1,2,4]triazol-1-yl-butoxy)phenyl]methyl]benzothiazole
- 25 - (2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)(4,5-dihydro-1*H*-imidazol-2-yl)amine
- *N*-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-*N'*-cyanoguanidine
- 30 - 6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine
- *N*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propyl)guanidine

- *N*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}propyl)guanidine
- 2-[(1-methylpiperidin-4-yloxy)[3-(4-morpholin-4-yl-butoxy)phenyl]methyl]benzothiazole
- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-2-yl)methanol
- 5 - (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-2-yl)methanol
- 6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hexylamine
- 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine
- 10 - 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}propylamine
- 4-(2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)piperazine-1-carboxylic acid *tert*-butyl ester
- 4-(2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)piperazine-1-carboxylic acid *tert*-butyl ester
- 15 - 2-[(1-methylpiperidin-4-yloxy)[3-(2-piperazin-1-yl-ethoxy)phenyl]methyl]benzothiazole
- 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}butylamine
- 2-[(1-methylpiperidin-4-yloxy)[3-(4-morpholin-4-yl-butoxy)phenyl]methyl]-1*H*-benzimidazole
- 20 - 2-[(1-methylpiperidin-4-yloxy)[3-(4-piperidin-1-yl-butoxy)phenyl]methyl]-1*H*-benzimidazole
- 2-[(2-fluoro-3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- *N-tert*-butoxycarbonyl-*N'*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pentyl)guanidine
- 25 - *N-tert*-butoxycarbonyl-*N'*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)guanidine
- 6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine
- 2-[(1-methylpiperidin-4-yloxy)[3-(1,2,3,6-tetrahydro-pyridin-4-yl)phenyl]methyl]-1*H*-benzimidazole
- 30 - *N-tert*-butoxycarbonyl-*N'*-(5-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-5-ynyl)guanidine

- *N*-(5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)guanidine
- *N*-*tert*-butoxycarbonyl-*N'*-(6-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine
- 5 - *N*-(6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine
- 4-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}butyl)piperazine-1-carboxylic acid *tert*-butyl ester
- 6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hexylamine
- 10 - *N*-*tert*-butoxycarbonyl-*N'*-(6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine
- *N*-(6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)guanidine
- 1-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-
- 15 3-isopropyl-thiourea
- 2-[(1-methylpiperidin-4-yloxy)[3-(3-[1,2,4]triazol-1-yl-propoxy)phenyl]methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(3-[1,2,3]triazol-2-yl-propoxy)phenyl]methyl]benzothiazole
- 20 - 2-[(1-methylpiperidin-4-yloxy)[3-(3-morpholin-4-yl-propoxy)phenyl]methyl]benzothiazole
- 4-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}propyl)piperazine-1-carboxylic acid *tert*-butyl ester
- 2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-
- 25 phenylsulfanyl}ethylamine
- 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}-3,6-dihydro-2*H*-pyridine-1-carboxamide
- 2-[[3-(2-chloroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- *N*-(6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hexyl)guanidine
- 30 - 2-[(1-methylpiperidin-4-yloxy)[3-(2-piperidin-1-yl-ethoxy)phenyl]methyl]-1*H*-benzimidazole

- *N-tert*-butoxycarbonyl-*N'*-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)guanidine
- *N*-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)guanidine
- 5 - 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine
- 4-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}propyl)piperazine-1-carboxylic acid *tert*-butyl ester
- (2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamino)acetic acid *tert*-butyl ester
- 10 - 4-(5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentyl)piperazine-1-carboxylic acid *tert*-butyl ester
- *N*-(6-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}hexyl)guanidine
- *N-tert*-butoxycarbonyl-*N'*-(6-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hexyl)guanidine
- 15 - *N*-(5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pentyl)guanidine
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}butylamine
- [[3-(4-aminobutoxy)phenyl](1*H*-benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propylamine
- 20 - 4-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethyl)piperazine-1-carboxylic acid *tert*-butyl ester
- (2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}ethylamino)acetic acid *tert*-butyl ester
- 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentylamine
- 25 - *N*-(4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine
- *N*-(3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)guanidine
- *N*-(4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}butyl)guanidine
- 30 - (5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentylamino)acetic acid *tert*-butyl ester
- 2-[(1-methylpiperidin-4-yloxy)(3-piperidin-4-ylethynyl-phenyl)methyl]-1*H*-benzimidazole

- 2-{{(1-methylpiperidin-4-yloxy)[3-(piperidin-4-ylmethoxy)phenyl]methyl}benzothiazole
- 2-{{(1-methylpiperidin-4-yloxy)[3-(piperidin-3-ylmethoxy)phenyl]methyl}benzothiazole
- 2-[[3-(1-methylpiperidin-3-ylmethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 5 - 2-[(1-methylpiperidin-4-yloxy)(3-piperidin-3-ylethynyl-phenyl)methyl]-1*H*-benzimidazole
- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}pentylamine
- 2-{{(1-methylpiperidin-4-yloxy)[3-(pyrrolidin-3-yloxy)phenyl]methyl}benzothiazole
- 2-{{(1-methylpiperidin-4-yloxy)[3-(pyrrolidin-3-yloxy)phenyl]methyl}benzothiazole
- 10 - 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-en-1-ol
- 3-amino-4-(2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamino)-cyclobut-3-ene-1,2-dione
- [[3-(6-aminohex-1-ynyl)phenyl](1*H*-benzimidazol-2-yl)methyl](1-methylpiperidin-4-yl)amine
- 15 - {[3-(4-aminobutoxy)phenyl]benzothiazol-2-yl-methyl}{(1-methylpiperidin-4-yl)amine}
- 2-[(3-azetidin-3-ylethynylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-en-1-ol
- 5-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-en-1-ol
- 4-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentyl)piperazine-1-carboxylic acid *tert*-butyl ester
- 20 - 2-[[3-(2-azetidin-3-ylethyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- *N*-(4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine
- 4-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidine-1-carboxamide
- 25 - 2-{{(1-methylpiperidin-4-yloxy)[3-(2-piperidin-2-yl-ethylsulfanyl)phenyl]methyl}-1*H*-benzimidazole
- 2-{{(1-methylpiperidin-4-yloxy)[3-(2-piperidin-4-yl-ethyl)phenyl]methyl}-1*H*-benzimidazole
- 30 - *N*-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pentyl)guanidine

- 2-[[3-[3-(3H-imidazol-4-yl)propylsulfanyl]phenyl](1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- *N-tert*-butoxycarbonyl-*N'*-(4-{3-[(benzothiazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}but-3-ynyl)guanidine
- 5 - 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentylamine
- *N*-acetyl-*N'*-(2-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine
- 2-[[3-(azetidin-3-yloxy)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}azetidin-3-ol
- 10 - (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)methanol
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-ylamine
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ol
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ol
- 15 - *N*-(1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)acetamide
- 2-[[3-(5-imidazol-1-ylpent-1-ynyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(5-pyrazol-1-yl-pent-1-ynyl)phenyl]methyl]-1H-benzimidazole
- 20 - 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-ol
- 2-[[3-[2-(1H-imidazol-4-yl)ethyl]phenyl](1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- acetic acid 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}piperidin-4-yl ester
- 25 - 2-[(3-bromo-phenyl)(1-methyl-pyrrolidin-3-ylmethoxy)methyl]-1H-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(piperidin-4-yloxy)phenyl]methyl]benzothiazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(5-[1,2,3]triazol-2-yl-pent-1-ynyl)phenyl]methyl]-1H-benzimidazole
- 30 - 2-[(1-methylpiperidin-4-yloxy)[3-(5-[1,2,3]triazol-1-yl-pent-1-ynyl)phenyl]methyl]-1H-benzimidazole

- *N*-(3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}prop-2-ynyl)guanidine
- *N*1-(5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenoxy}pentyl)butane-1,4-diamine
- 5 - {3-(6-aminohex-1-ynyl)phenyl}benzothiazol-2-yl-methyl}{(1-methylpiperidin-4-yl)amine
- 5-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-enylamine
- 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}but-2-en-1-ol
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ylamine
- 10 - 2-[(2,5-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(2-fluoro-5-iodo-phenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 3-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylethynyl}azetidine-1-carboxamidine
- 4-{3-[(5-fluoro-1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol
- 15 - 2-{3-[(5-fluoro-1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethylamine
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ylamine
- 2-[[3-(3-fluoropyrrolidin-1-yl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole
- 20 - 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}but-2-enylamine
- 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole
- 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole (enantiomer A)
- 25 - 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1*H*-benzimidazole (enantiomer B)
- *N*-(2-aminoethyl)-2-{3-[(1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetamide
- *N*-(2-{3-[(5-fluoro-1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)guanidine
- 30 - 2-(5-{3-[(5-fluoro-1*H*-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)isoindole-1,3-dione

- 6-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine oxalate
- 4-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine oxalate
- 5 - N-(3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}propyl)guanidine, dihydrochloride
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-one, oxalate
- N-(4-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butyl)guanidine, dihydrochloride
- 10 - 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}pentan-1-ol
- N-(2-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-N-(2,2-dimethylpropionyl)guanidine
- 15 - 2-[(1-methylpiperidin-4-yloxy)(4-nitrophenyl)methyl]-1H-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)[3-(pyridin-3-yloxy)phenyl]methyl]benzothiazole, oxalate
- 2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]-5-fluoro-1H-benzimidazole, oxalate
- 4-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]aniline
- 20 - 4-[(1H-benzimidazol-2-yl)(piperidin-4-yloxy)methyl]aniline, hydrochloride
- N-(2-amino-ethyl)-2-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}acetamide
- 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}-3-trifluoromethylpyrrolidin-3-ol, oxalate
- 25 - 2-[[3-(4,5-dihydro-1H-imidazol-2-ylmethylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[[3-(4,5-dihydro-1H-imidazol-2-ylmethylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole
- 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5,6-difluoro-1H-benzimidazole
- 30 - 2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1-methyl-1H-benzimidazole, dioxalate

- 2-amino-5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}-1,5-dihydroimidazol-4-one
- 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5,6,7-trifluoro-1H-benzimidazole
- 1-(2-ethoxyethyl)-2-[(3-iodophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, dioxalate
- 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]benzaldehyde
- 4-{3-[(1H-benzimidazol-2-yl)(1-methylazetidin-3-ylmethoxy)methyl]phenylsulfanyl}butylamine, oxalate
- 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzoxazole, oxalate
- {3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}methanol. dimethylsulfoxonium ylide of 3-bromophenylacetic acid methyl ester
- 2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer B
- 2-[(2,6-difluoro-3-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole ethyl (6-{3-[(1-methyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynyl)carbamate, oxalate
- 2-[(1H-indol-6-yl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 2-[benzo[b]thiophen-6-yl(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer B
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol
- 2-[(1H-benzimidazol-2-yl)hydroxymethyl]phenol
- 2-[(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylimino)phenylmethyl]phenol
- 5-(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylimino)-2-methylcyclopent-1-enol
- 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, enantiomer B
- 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine, enantiomer A

- 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine, enantiomer B
- 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole, enantiomer A
- 5 - 2-[(3-bromophenyl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-1H-benzimidazole, enantiomer B
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-methylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol enantiomer A
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol enantiomer B
- 10 - 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol enantiomer A
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol enantiomer B
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol enantiomer A
- 15 - 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol enantiomer B
- 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}pent-4-ynylamine, dioxalate
- 20 - 3-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}cyclopentylamine, oxalate
- 2-[[3-(3-fluoropyrrolidin-1-yl)phenyl](1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate
- 5-{3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpyrrolidin-3-ylmethoxy)methyl]phenyl}pent-4-ynylamine, oxalate
- 25 - 2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]benzothiazole, oxalate (one epimer)
- 2-[(3-bromophenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]benzothiazole, oxalate (50/50 mixture of two epimers)
- 30 - 2-[(1-methylpiperidin-4-yloxy)[3-(octahydrocyclopenta[c]pyrrol-5-yloxy)phenyl]methyl]benzothiazole, dioxalate

- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)methylamine, dioxalate
- 4-{3-[(5,6-difluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butan-1-ol
- 5 - 2-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}octahydrocyclopenta[c]pyrrol-5-ylamine, dioxalate
- 2-{[3-(3-fluoropropoxy)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, oxalate
- 2-{[3-(2-fluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, oxalate
- 10 - 4-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenoxy}cyclohexylamine, oxalate
- 6-{3-[(1-methyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine, dioxalate
- 15 - 1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-2-ylmethylamine, oxalate
- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)(methyl)amine, oxalate
- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-yl)(dimethyl)amine, oxalate
- 20 - 2-{[3-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2-yl)phenyl](1-methylpiperidin-4-yloxy)methyl}benzothiazole, dioxalate
- 2-[(2-fluoro-5-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 25 - 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenol, oxalate
- 2-{[2-fluoro-5-(2-fluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, oxalate
- 2-[(2-fluoro-5-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 30 - 4-{3-[(1-methylpiperidin-4-yloxy)(5,6,7-trifluoro-1H-benzimidazol-2-yl)methyl]phenylsulfanyl}butylamine, oxalate

- 4-{3-[(5,6-difluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}butylamine, oxalate
- 6-(3-{[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl](1-methylpiperidin-4-yloxy)methyl}phenyl)hex-5-ynylamine, dioxalate
- 5 - 6-(3-{[1-(2-methoxyethyl)-1H-benzimidazol-2-yl](1-methylpiperidin-4-yloxy)methyl}phenyl)hex-5-ynylamine, dioxalate
- 2-{[3-(3-fluoropropylsulfanyl)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, dioxalate
- 5-fluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 10 - 4,5,6-trifluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 5,6-difluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 15 - 2-{[2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole
- 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(2-chloro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 20 - 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate
- 2-[(4-chloro-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 7-fluoro-2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 25 - 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate
- 2-[(4-chloro-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]benzothiazole, oxalate
- 2-[(3-ethoxy-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 30 - 2-[(2,6-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzoxazole, oxalate
- 2-[(1-methylpiperidin-4-yloxy)(4-trifluoromethylphenyl)methyl]-1H-benzimidazole

- 2-[(2-fluoro-4-trifluoromethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(2,4-dimethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(3-methoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 5 - 2-[chroman-7-yl(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]benzoxazole, oxalate
- 2-[(3,5-bis-trifluoromethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 5-fluoro-2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 10 - 2-[(2,3-difluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(3-chloro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- ethyl 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]benzimidazole-1-carboxylate, oxalate
- 15 - 2-[(3-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(5-bromo-2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}hex-5-ynylamine, oxalate
- 5-{4-fluoro-3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynylamine
- 20 - ethyl (5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenyl}pent-4-ynyl)carbamate
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-chlorophenol
- ethyl (5-{4-fluoro-3-[(5-fluoro-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pent-4-ynyl)carbamate
- 25 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-trifluoromethoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-methoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-methylphenol
- 30 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-bromophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-ethoxyphenol
- 2-[(1H-indol-7-yl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole

- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,6-difluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,6-dichlorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-fluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-fluorophenol
- 5 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,5-difluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-fluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-chlorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-methylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-methylsulfanylphenol
- 10 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-ethylsulfanylphenol
- 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]biphenyl-4-ol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-tert-butylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-propylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-methoxyphenol
- 15 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-fluoro-5-methylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-chlorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-fluoro-4-ethylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-benzylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-trifluoromethylphenol
- 20 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-chloro-6-fluorophenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-fluoro-3-methylphenol
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3-methylphenol
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]indan-5-ol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-propoxyphenol
- 25 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(1-methyl-1-phenylethyl)phenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(2-fluoroethoxy)phenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(3-fluoropropoxy)phenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluoro-6-methylphenol
- 30 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-fluoro-4-methoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-phenoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluoro-6-methoxyphenol

- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4,5-dimethylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(3-fluoropropylsulfanyl)phenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-fluoro-5-methylphenol
- 5 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-(2-fluoroethylsulfanyl)phenol
- 3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-hydroxybiphenyl
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-ethylphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-trifluoromethylphenol
- 10 - 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-4-hydroxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5,6,7,8-tetrahydro-1-naphthol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-6-trifluoromethoxyphenol
- 2-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-5-trifluoromethoxyphenol
- 15 - 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2-fluoro-3,4-dimethylphenol
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-3-fluoro-2-methylphenol
- 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,4-difluoro-3-methylphenol
- 20 - 6-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]-2,3-difluorophenol
- (1-{3-[benzothiazol-2-yl(1-methylpiperidin-4-yloxy)methyl]phenyl}-azetidin-3-yl)dimethylamine, oxalate
- 1-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}pyrrolidin-3-ol, oxalate
- 25 - 2-[(1-methylpiperidin-4-yloxy)[3-(pyrrolidin-3-yloxy)phenyl]methyl]-1H-benzimidazole, dioxalate
- 2-[(5-chloro-2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 2-[(2-fluoro-5-trifluoromethylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-
- 30 benzimidazole, oxalate
- 6-{3-[(1-ethyl-1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}hex-5-ynylamine,oxalate

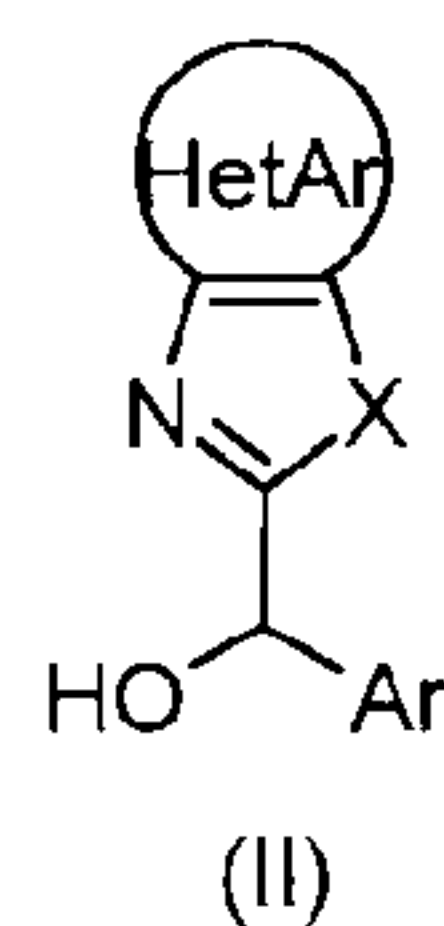
- 2-[(2-fluoro-5-methoxyphenyl)(1-methylpyrrolidin-3-ylmethoxy)methyl]-1H-benzimidazole, oxalate
- 2-[(1-methylpiperidin-4-yloxy)(3-trifluoromethylsulfanylphenyl)methyl]-1H-benzimidazole, oxalate
- 5 - 2-[(4-fluoro-3-trifluoromethoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 2-[(2-fluoro-5-propoxyphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole, oxalate
- 4-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenol
- 10 - 2-{[3-(3,3-difluoropyrrolidin-1-yl)phenyl](1-methylpiperidin-4-yloxy)methyl}-1H-benzimidazole, dioxalate
- 2-{[3-(5-fluorohexahydrocyclopenta[c]pyrrol-2-yl)phenyl](1-methylpiperidin-4-yloxy)methyl}benzothiazole, dioxalate
- 6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexylamine, oxalate
- 15 - 5-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}oxazolidin-2-one
- N-(6-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}hexyl)guanidine, dihydrochloride
- 20 - 4-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}but-2-enylamine
- 4-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}but-2-enylamine, oxalate
- N-(2-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanyl}ethyl)-N-isobutyrylguanidine
- 25 - 3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}allylamine
- cis-2-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenylsulfanylmethyl}cyclopropylmethylamine
- N-(3-{3-[(1H-benzimidazol-2-yl)(1-methylpiperidin-4-yloxy)methyl]phenyl}allyl)guanidine, trihydrochloride
- 30 - 2-[(azetidin-3-ylmethoxy)(3-bromophenyl)methyl]-1H-benzimidazole
- 2-[(3-bromophenyl)(1-methylazetidin-3-ylmethoxy)methyl]-1H-benzimidazole

- 2-[(2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(2-fluoro-4-methylphenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(5-ethylsulfanyl-2-fluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(azetidin-3-ylmethoxy)(2-fluoro-5-trifluoromethoxyphenyl)methyl]-1H-benzimidazole,
5 oxalate
- 2-[(2-fluoro-5-trifluoromethoxyphenyl)(1-methylazetidin-3-ylmethoxy)methyl]-1H-benzimidazole, oxalate
- 2-[(3-ethylsulfanyl-2,6-difluorophenyl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 10 - 2-[(2,2-difluorobenzo[1,3]dioxol-5-yl)(1-methylpiperidin-4-yloxy)methyl]-1H-benzimidazole
- 2-[(piperidin-4-yloxy)thiophen-3-ylmethyl]-1H-benzimidazole
- 2-[(1-methylpiperidin-4-yloxy)thiophen-3-ylmethyl]-1H-benzimidazole
- 2-[(piperidin-4-yloxy)thiophen-2-ylmethyl]-1H-benzimidazole, and
- 15 - 2-[(1-methylpiperidin-4-yloxy)thiophen-2-ylmethyl]-1H-benzimidazole

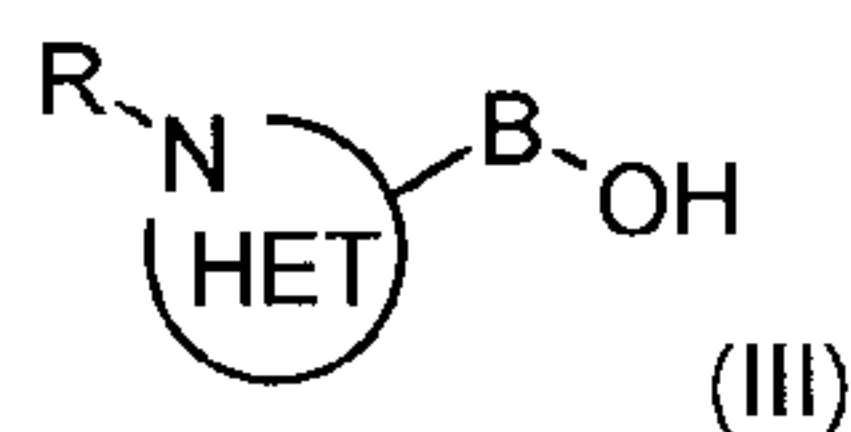
as well as their enantiomers, diastereomers, mixtures thereof and pharmaceutically acceptable salts, free forms, tautomers, hydrates and solvates.

- 20 9. Process of preparation of a compound of formula (I) according to any one of claims 1 to 8 wherein

- where A = O said process comprises the step of etherification of compound of formula (II)

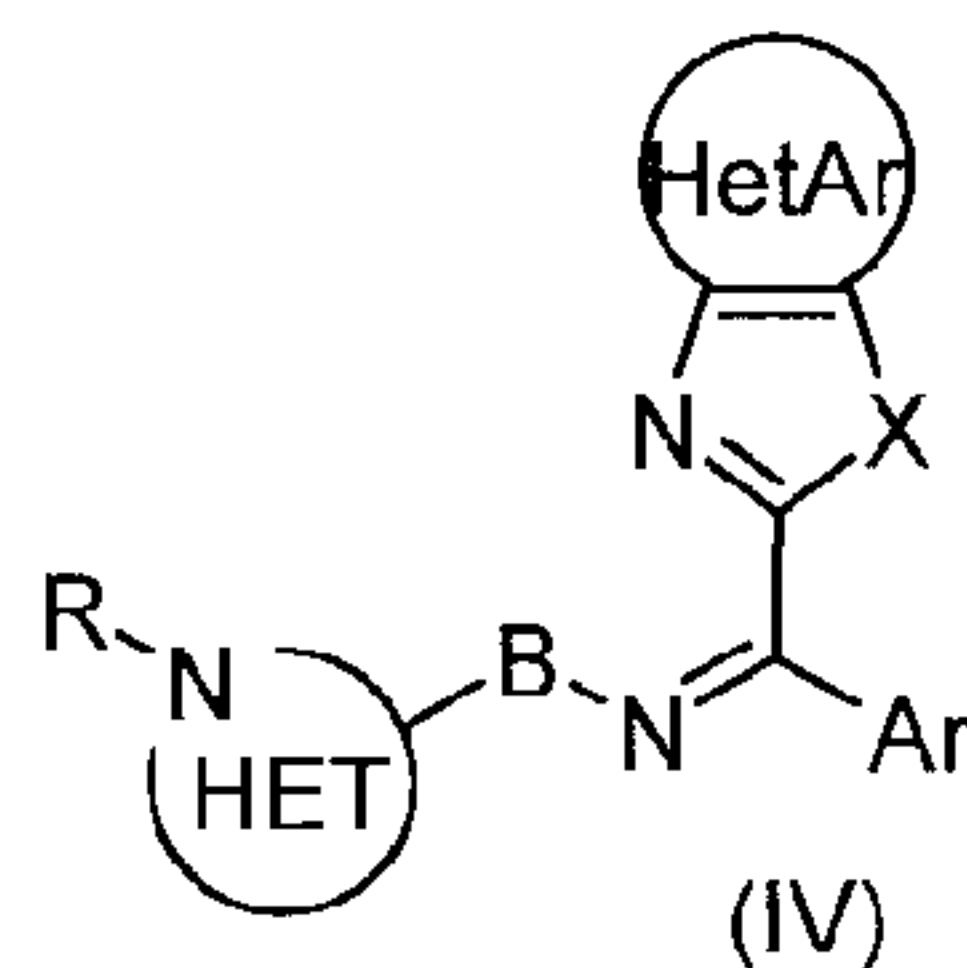


- 25 in which X, HetAr and Ar are as defined in anyone of claims 1 to 8 with a compound of formula (III)



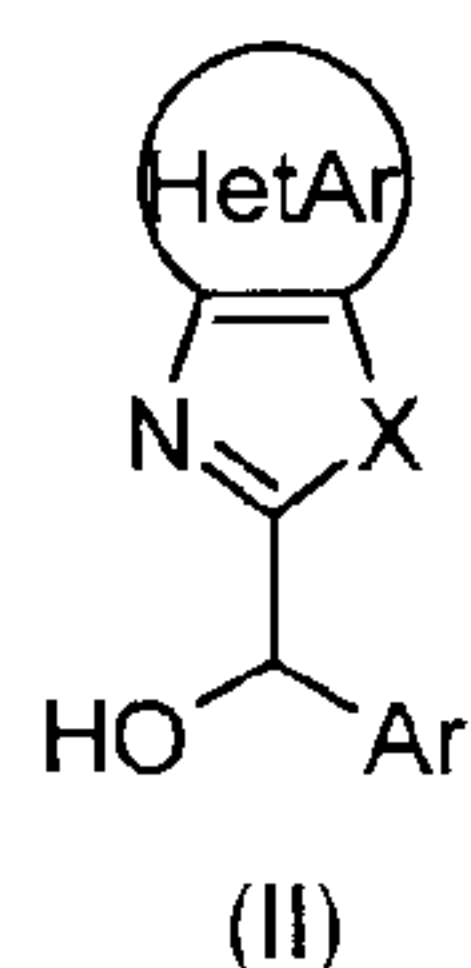
in which R, HET and B are as defined in in any one of claims 1 to 8; or

- where A = NH said process comprises the step of reduction of a compound of formula (IV)



5 in which R, HET, B, X, HetAr and Ar are as defined in any one of claims 1 to 8; or

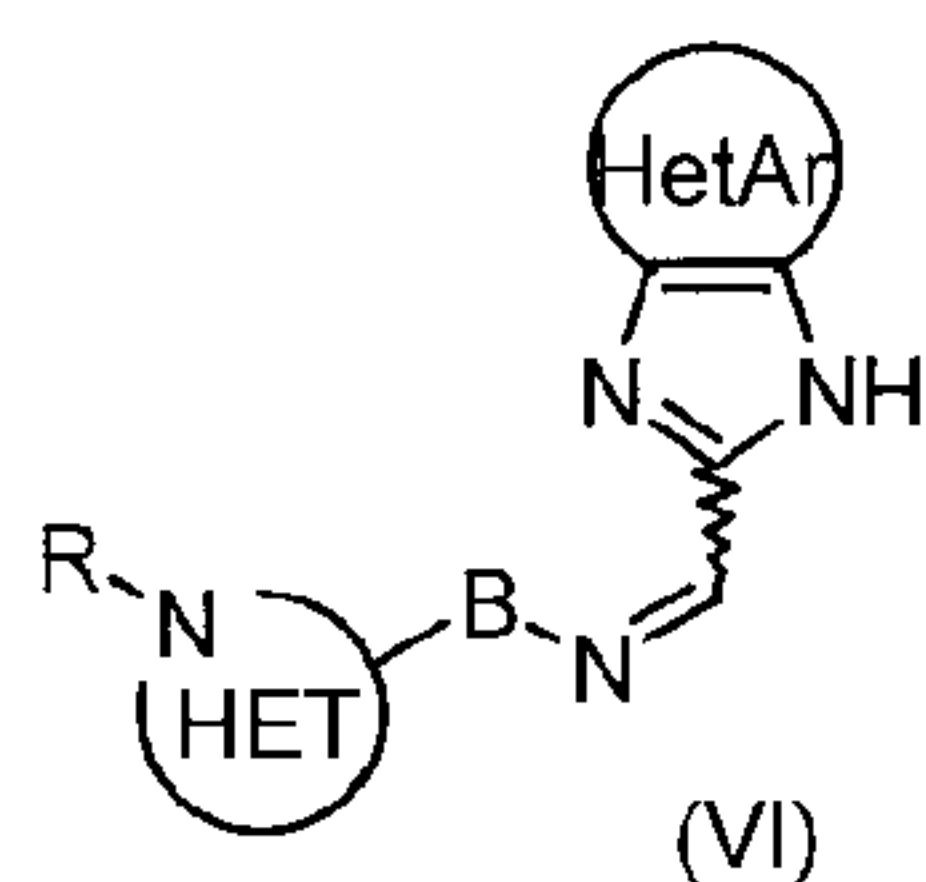
- where A = NH said process comprises the step of condensation of compound of formula (II)



in which X, HetAr and Ar are as defined in any one of claims 1 to 8

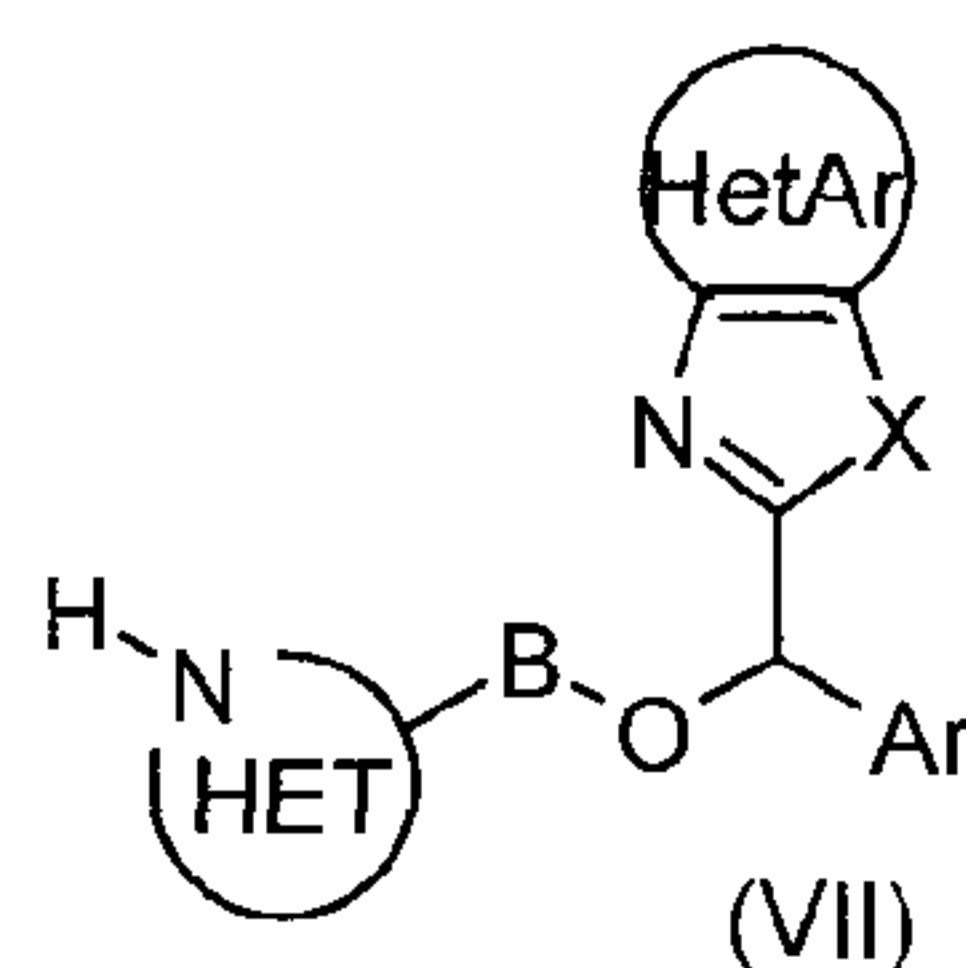
10 with an amine ; or

- where A and X are NH said process comprises the step of condensing an organometallic reagent ArM onto a compound of formula (VI):



in which R, HET, B, HetAr and Ar are as defined in any one of claims 1 to 8; or

15 - where A=O said process comprises the step of alkylation of compound of formula (VII)



in which HET, B, X, HetAr and Ar are as defined in any one of claims 1 to 8.

- 5 10. The process according to claim 9 further comprising the additional step of isolating the desired compound.
11. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 8 with a pharmaceutically acceptable excipient.
- 10 12. The compound according to any one of claims 1 to 8 for use in treatment and/or prevention of a disease associated with H₄ dysfunction.
- 15 13. The compound for use according to claim 12 for the treatment or prevention of a respiratory disease ; a disorder of the genito-urinary tract ; a dermatological disease ; a disease of the cardiovascular system ; a disease of the gastrointestinal tract ; an autoimmune and inflammatory disease ; cancer; pain; chronic hypereosinophilias; a chronic disease associated with mast-cell multiplication; or a lymphatic system disease.
- 20 14. The compound for use according to claim 13, wherein the respiratory disease is selected from the group consisting of respiratory inflammatory diseases, adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis, chronic sinusitis, allergy, allergy induced airway responses,

25 allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, conjunctivitis, nasal congestion, and allergic congestion.
15. The compound for use according to claim 13, wherein the disorder of the genito-urinary tract is selected from the group consisting of female and male sexual

dysfunction, overactive bladder conditions, urinary incontinence, bladder overactivity, benign prostate hyperplasia and lower urinary tract symptoms.

- 5 16. The compound for use according to claim 13, wherein the dermatological disease is selected from the group consisting of dermatitis, psoriasis and itchy skin.
- 10 17. The compound for use according to claim 13, wherein the disease of the cardiovascular system is selected from the group consisting of thromboembolic diseases, atherosclerosis, myocardial infarction, angina pectoris, myocardial ischaemia and arrhythmia, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses, hypotension, pulmonary hypertension, malignant hypertension, cardiac insufficiency, heart or kidney failure, stroke and renal dysfunction.
- 15 18. The compound for use according to claim 13, wherein the disease of the gastrointestinal tract is selected from the group consisting of inflammatory bowel disease, Crohn's disease, ulcerative colitis, and food allergy.
- 20 19. The compound for use according to claim 13, wherein the autoimmune and inflammatory disease is selected from the group consisting of rheumatoid arthritis, and multiple sclerosis.
- 25 20. A combination of a compound according to any one of claims 1 to 8 with one or more therapeutic agent(s) selected from:
- Histamine H₁, H₂ or H₃ receptor antagonists,
 - Leukotriene antagonists,
 - 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists
 - 30 • CX₁- and α_2 -adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use
 - Xanthines,
 - Steroidal or non-steroidal antiinflammatories,

- Ketotifen
- COX-1 inhibitors (NSAIDs) and COX-2 selective inhibitors
- Immunosuppressants
- mucolytics or anti-tussive agents.

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21. The combination according to claim 20, wherein the xanthines are a theophylline or an aminophylline.

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22. The combination according to claim 20, wherein the steroidal or anti-steroidal anti-inflammatories are a cromoglycate or a nedocromil sodium.

23. The combination according to claim 20, wherein the H₁ receptor antagonist is cetirizine, desloratadine, bepotastine or doxepin.

