Abstract: The present invention is concerned with heteroaryl-cyclohexyl-tetraazabenzo[e]azulenes of formula (I) wherein R¹, R² and R³ are as described herein. The compounds according to the invention act as Via receptor modulators, and in particular as Via receptor antagonists, their manufacture, pharmaceutical compositions containing them and their use as medicaments. The active compounds of the present invention are useful as therapeutics acting peripherally and centrally in the conditions of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.
Case 26636

HETEROARYL - CYCLOHEXYL - TETRAAZABENZO [E] AZULENES AS VASOPRESSIN VIA RECEPTOR ANTAGONISTS

Background of the invention

Vasopressin is a 9 amino acid peptide mainly produced by the paraventricular nucleus of the hypothalamus. In the periphery vasopressin acts as a neurohormone and stimulates vasoconstriction, glycogenolysis and antiureasis.

Three vasopressin receptors, all belonging to the class I G-protein coupled receptors, are known. The Via receptor is expressed in the brain, liver, vascular smooth muscle, lung, uterus and testis, the Vlb or V3 receptor is expressed in the brain and pituitary gland, the V2 receptor is expressed in the kidney where it regulates water reabsorption and mediates the antidiuretic effects of vasopressin (Robben, et al. (2006). Am J Physiol Renal Physiol. 291, F257-70, "Cell biological aspects of the vasopressin type-2 receptor and aquaporin 2 water channel in nephrogenic diabetes insipidus"). Compounds with activity at the V2 receptor can therefore cause side-effects on blood homeostasis.

The oxytocin receptor is related to the Vasopressin receptor family and mediates the effects of the neurohormone oxytocin in the brain and the periphery. Oxytocin is believed to have central anxiolytic effects (Neumann (2008). J Neuroendocrinol. 20, 858-65, "Brain oxytocin: a key regulator of emotional and social behaviors in both females and males"). Central oxytocin receptor antagonism might therefore lead to anxiogenic effects, which are regarded as undesired side-effects.

In the brain vasopressin acts as a neuromodulator and is elevated in the amygdala during stress (Ebner, et al. (2002). Eur J Neurosci. 15, 384-8., "Forced swimming triggers vasopressin release within the amygdala to modulate stress-coping strategies in rats"). It is known that stressful life events can trigger major depression and anxiety (Kendler, et al. (2003). Arch Gen Psychiatry. 60, 789-96, "Life Event Dimensions of Loss, Humiliation, Entrapment, and Danger in the Prediction of Onsets of Major Depression and Generalized Anxiety") and that both have very high comorbidity, with anxiety often preceding major depression (Regier, et al. (1998). Br J Psychiatry Suppl. 24-8, "Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders"). The Via receptor is extensively expressed in the brain and particularly in limbic areas like the amygdala, lateral septum and hippocampus which are playing an important role in the regulation of anxiety. Indeed Via knock-out mice show a reduction in anxious behavior in the plus-maze, open field and light-dark box (Bielsky, et al. (2004). Neuropsychopharmacology. 29, 483-93, "Profound impairment in social recognition and reduction in anxiety-like behavior in vasopressin Via receptor knockout mice"). The downregulation of the Via receptor using antisense oligonucleotide injection in the septum also causes a reduction in anxious behavior (Landgraf, et al. (1995). Regul Pept. 59, 229-39,. "VI vasopressin receptor antisense oligodeoxynucleotide into septum reduces vasopressin binding,

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The Via receptor is also mediating the cardiovascular effects of vasopressin in the brain by centrally regulating blood pressure and heart rate in the solitary tract nucleus (Michelini and Morris (1999). Ann N Y Acad Sci. 897, 198-211, "Endogenous vasopressin modulates the cardiovascular responses to exercise"). In the periphery it induces the contraction of vascular smooth muscles and chronic inhibition of the Via receptor improves hemodynamic parameters in myocardial infarcted rats (Van Kerckhoven, et al. (2002). Eur J Pharmacol. 449, 135-41, "Chronic vasopressin V(1A) but not V(2) receptor antagonism prevents heart failure in chronically infarcted rats"). Hence, Via antagonists with improved penetration through the blood-brain barrier are expected to be of advantage.

A vasopressin Via receptor antagonist was shown to be effective in reducing dysmenorrhea in the clinic (Brouard, et al. (2000). Bjog. 107, 614-9, “Effect of SR49059, an orally active Via vasopressin receptor antagonist, in the prevention of dysmenorrhea”). Via receptor antagonism has also been implicated in the treatment of female sexual dysfunction (Aughton, et al. (2008). Br J Pharmacol. doi:10.1038/bjp.2008.253, "Pharmacological profiling of neuropeptides on rabbit vaginal wall and vaginal artery smooth muscle in vitro"). In a recent study Via receptor antagonists were suggested to have a therapeutic role in both erectile dysfunction and premature ejaculation (Gupta, et al. (2008). Br J Pharmacol. 155, 118-26, "Oxytocin-induced contractions within rat and rabbit ejaculatory tissues are mediated by vasopressin V(1A) receptors and not oxytocin receptors").

**Field of the invention**

The present invention is concerned with heteroaryl-cyclohexyl-tetraazabenzo[e]azulenes, which act as Via receptor modulators, and in particular as Via receptor antagonists, their manufacture, pharmaceutical compositions containing them and their use as medicaments.
Summary of the invention

The present invention provides compounds of formula I useful for acting peripherally and centrally in the conditions of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

In particular, the present invention is concerned with compounds of formula I

![Chemical Structure]

wherein R\(^1\), R\(^2\) and R\(^3\) are as described in herein.

Detailed description of the invention

The present invention provides compounds which act as Via receptor modulators, and in particular as Via receptor antagonists. It is a further object of the invention to provide selective inhibitors of the Via receptor since it is expected that selectivity affords a low potential to cause unwanted off-target related side effects such as discussed above.

Such Via antagonists are useful as therapeutics acting peripherally and centrally in the conditions of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior. Particular indications with regard to the present invention are the treatment of anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

The Via activity can be detected as described in the experimental section.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the terms "Ci-ealkyl", alone or in combination with other groups, stands for a hydrocarbon radical that is linear or branched, with single or multiple branching, wherein the alkyl group contains 1 to 6 carbon atoms, for example, methyl (Me), ethyl (Et), propyl,
isopropyl (j-propyl), w-butyl, j-butyl (iso-butyl), 2-butyl (sec-butyl), i-butyl (iert-butyl) and the like. Particular alkyl groups are groups with 1 to 4 carbon atoms. More particular are methyl, ethyl and isopropyl.

The term "Ci-alkoxy", alone or in combination with other groups, denotes a group -O-R' wherein R' is Ci-alkyl as defined above, for example methoxy, ethoxy, propoxy, iert-butoxy and the like. Particular alkoxy groups are groups with 1 to 4 carbon atoms. Most particular is methoxy.

The term "6-membered heteroaryl ring", alone or in combination with other groups, refers to a monocyclic aromatic group having a single 6 membered ring, and containing 1, 2 or 3 heteroatoms independently selected from O, S and N. Particular single 6 membered heteroaryl rings have 1 or 2 N. Examples include pyridinyl, pyrimidinyl, pyrazinyl, thiazinyl, oxazinyl and the like. Particular single 6-membered rings are pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl. Specific "6-membered heteroaryl ring" are attached via a carbon atom to the cyclohexyl-moiety. Examples are pyridine-2-yl, pyridine-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrazin-2-yl, pyridazin-2-yl and pyrazin-3-yl.

The term "cycloalkyl" refers to a 3 to 8 membered carbon ring, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Particular are cycloalkyl groups having a 3, 4, 5 or 6 membered carbon ring. Specific is cyclobutyl.

The term "heterocyclyl" refers to a 3 to 7-membered heterocyclic ring containing at least one heteroatom, such as N, O or S, the number of N atoms being 0, 1, 2 or 3 and the number of O and S atoms each being 0, 1 or 2. Examples of heterocyclyl groups include pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl, tetrahydropyrindinyl, tetrahydropropyrl, azetidinyl, thiazolidinyl, oxazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, azepanyl, diazepanyl, oxazepanyl and the like.

The term "cyano" denotes the group -CN.

The term "hydroxy" denotes the group -OH.

The term "oxo" denotes the group =O.

The term "Boc" denotes the group -C(0)OC(CH$_3$)$_3$.

The term "S(0)2-C$_{1,5}$-alkyl" refers to an "Ci-6-alkyl" as defined herein linked via an -S(0)$_2$-.

The term "C(0)-C$_{1,5}$-alkyl" refers to an "Ci-6-alkyl" as defined herein linked via an -C(=0)-.
The term "C(0)0-C,alkyl" refers to an "Ci,alkyl" as defined herein linked via an C(=O)0-.

The term "halogen", alone or in combination with other groups, denotes chloro (Cl), iodo (I), fluoro (F) and bromo (Br). Particular halogens are F and Cl. Specific is Cl.

The term "halogen-Ci,alkyl", alone or in combination with other groups, refers to a Ci,alkyl group as defined above substituted by one or multiple halogen, in particular F (i.e. fluoro-Ci,alkyl), for example the following groups: CF₃, CHF₂, CH₂F, CH₂CF₃, CH₂CH₂CF₃, CF₂CHF₂, and the like. Particular is CF₃.

The term "hydroxy-Ci,alkyl", alone or in combination with other groups, refers to a Ci,alkyl group as defined above substituted by one or multiple hydroxy, for example the following groups: -CH₂OH, -CH₂CH₂OH, and the like. Particular is -CH₂CH₂OH.

The term "halogen-Ci,alkoxy", alone or in combination with other groups, refers to a Ci,alkoxy group as defined above substituted by one or multiple halogen as defined herein, in particular F (i.e. fluoro-Ci,alkoxy), for example the following group: CF₃-CH₂-O-.

The term "pharmaceutically acceptable salt" refers to salts that are suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response, and the like. Examples of suitable salts with inorganic and organic acids are, but are not limited to, hydrochloric acid, nitric acid, sulphuric acid, phosphoric acid, sulphuric acid, citric acid, formic acid, fumaric acid, maleic acid, lactic acid, malic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulphonic acid, trifluoroacetic acid and the like. Particular are hydrochloric acid and formic acid. Specific "pharmaceutically acceptable salts" are mono-hydrochloride, di-hydrochloride and formate.

The terms "pharmaceutically acceptable carrier" and "pharmaceutically acceptable auxiliary substance" refer to carriers and auxiliary substances such as diluents or excipients that are compatible with the other ingredients of the formulation.

The term "pharmaceutical composition" encompasses a product comprising specified ingredients in pre-determined amounts or proportions, as well as any product that results, directly or indirectly, from combining specified ingredients in specified amounts. Particularly it encompasses a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product that results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.
The term "inhibitor" denotes a compound which competes with, reduces or prevents the binding of a particular ligand to particular receptor or which reduces or prevents the inhibition of the function of a particular protein.

The term "half maximal inhibitory concentration" (IC_{50}) denotes the concentration of a particular compound required for obtaining 50% inhibition of a biological process in vitro. IC_{50} values can be converted logarithmically to pIC_{50} values (-log IC_{50}), in which higher values indicate exponentially greater potency. The IC_{50} value is not an absolute value but depends on experimental conditions e.g. concentrations employed. The IC_{50} value can be converted to an absolute inhibition constant (Ki) using the Cheng-Prusoff equation (Biochem. Pharmacol. (1973) 22:3099). The term "inhibition constant" (Ki) denotes the absolute binding affinity of a particular inhibitor to a receptor. It is measured using competition binding assays and is equal to the concentration where the particular inhibitor would occupy 50% of the receptors if no competing ligand (e.g. a radioligand) was present. Ki values can be converted logarithmically to pKi values (-log Ki), in which higher values indicate exponentially greater potency.

The term "as defined herein" and "as described herein" when referring to a variable incorporates by reference the broad definition of the variable as well as preferred, more preferred and most preferred definitions, if any.

The terms "treating", "contacting" and "reacting" when referring to a chemical reaction means adding or mixing two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.


The term "pharmaceutically acceptable excipient" denotes any ingredient having no therapeutic activity and being non-toxic such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants or lubricants used in formulating pharmaceutical products.

"Therapeutically effective amount" means an amount that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

The following table lists abbreviations used within the present document.
(BOC)$_2$O  \(\text{di-}t\text{ert-}b\text{uty}l\ \text{pyrocarbonate}\)

(COCl)$_2$  \(\text{o}x\text{alyl (di)chloride}\)

AcOH  \(\text{acetic acid}\)

CH$_2$Cl$_2$  \(\text{dichloromethane}\)

((CH$_3$)$_3$CCO)$_2$O  trimethylacetic anhydride

CuCl  \(\text{copper(I) chloride}\)

DMF  \(\text{dimethylformamide}\)

DMAP  \(4-(\text{dimethylamino})\)-pyridine\)

DMSO  \(\text{dimethylsulfoxide}\)

(dppf)/PdCl$_2$  \([1,1\text{'-Bis(diphenylphosphino)ferrocene}]\) dichloropalladium(II).

EDTA  \(\text{ethylene diamine tetraacetate}\)

EtN$_3$  \(\text{triethylamine}\)

EtOAc  \(\text{ethyl acetate}\)

EtOH  \(\text{ethanol}\)

HATU  \(2-(7\text{-aza- 1H-benzotriazole- 1-yl})-1,1,3,3\text{-tetramethyluronium hexafluorophosphate}\)

HEPES  \(2-(4-(2\text{-hydroxyethyl})\text{-1-piperazinyl})\text{-ethanesulfonic acid}\)

HF-pyridine  \(\text{pyridine hydrofluoride}\)

H$_2$O  \(\text{water}\)

H$_2$SO$_4$  \(\text{sulphuric acid}\)

HPLC  \(\text{high performance liquid crystallography}\)

KHF$_2$  \(\text{potassium bifluoride}\)

K$_3$P$_2$O$_4$  \(\text{potassium phosphate}\)

Lawesson's reagent  \(2,4\text{-bis-(4-methoxyphenyl)-1,3,2,4-dithiapiposphetane-2,4-disulfide}\)

MeOH  \(\text{methanol}\)

MS  \(\text{mass spectroscopy}\)

Na$_2$CO$_3$  \(\text{sodium carbonate}\)

NaN$_2$O$_2$  \(\text{sodium nitrite}\)
The invention also provides pharmaceutical compositions, methods of using, and methods of preparing the aforementioned compounds.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes can be made and equivalents can be substituted without departing from the true spirit and scope of the invention. In addition, many modifications can be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto. All separate embodiments can be combined.

The compounds of formula I can contain asymmetric carbon atoms. Accordingly, the present invention includes all stereoisomeric forms of the compounds of formula I, including
each of the individual stereoisomers and mixtures thereof, i.e. their individual optical isomers and mixtures thereof. Additional asymmetric centers can be present depending upon the nature of the various substituents on the molecule. Each such asymmetric centre will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within this invention. The present invention is meant to comprehend all such isomeric forms of these compounds. The independent syntheses of these diastereomers or their chromatographic separations can be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry can be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric centre of known absolute configuration. If desired, racemic mixtures of the compounds can be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography.

This applies in particular to the heteroaryl-head group (HG) of the compounds of formula I, namely

![Diagram](image)

wherein at least the carbon atoms 1 and 4 are asymmetric carbon atoms and \(R^3\) could further comprise asymmetric carbon atoms. It is to be understood that present invention includes all individual stereoisomers of head groups and mixtures thereof.

In particular, these head groups HG are

![Diagram](image)

\(trans\)  \(cis\)
It is further understood that all embodiments of the invention as described herein can be combined with each other.

In detail, the present invention is concerned with compounds of formula I

\[
\begin{align*}
\text{I} & \\
R^1, R^2, R^3 & \\
\end{align*}
\]

wherein

\( R^1 \) is selected from the group consisting of

1. \( \text{H} \),
2. \(-\text{Ci}_6\text{-alkyl}, \) unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of OH, halogen, cyano and \( \text{Ci}_6\text{-alkoxy} \),
3. \(-\text{S}(0)\text{2-Ci}_6\text{-alkyl}, \) wherein the \( \text{Ci}_6\text{-alkyl} \) is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of OH, halogen, cyano and \( \text{Ci}_6\text{-alkoxy} \),
4. \(-\text{C}(0)\text{-Ci}_6\text{-alkyl}, \) wherein the \( \text{Ci}_6\text{-alkyl} \) is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of OH, halogen, cyano and \( \text{Ci}_6\text{-alkoxy} \),
5. \(-\text{C}(0)\text{0-Ci}_6\text{-alkyl}, \) wherein the \( \text{Ci}_6\text{-alkyl} \) is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of OH, halogen, cyano and \( \text{Ci}_6\text{-alkoxy} \),
6. cycloalkyl, unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of OH, halogen, cyano, \( \text{Ci}_6\text{-alkyl} \) and \( \text{Ci}_6\text{-alkoxy} \),
7. \( \text{S}(0)\text{2-(CH}_2)_q\text{-NR}^\text{iR}^\text{ii} \), wherein

\( q \) is 0 or 1,

\( R^1 \) and \( R^\text{ii} \) is each individually selected from the group consisting of \( \text{H} \) and \( \text{Ci}_6\text{-alkyl} \), or \( R^1 \) and \( R^\text{ii} \) form together with the nitrogen to which they are attached a 3- to 7-membered heterocyclyl containing one or two heteroatoms individually selected from
N, O and S, and which heterocyclyl is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of oxo, halogen, C\textsubscript{1-6}-alkyl and Cl\_6-alkoxy,

viii) -(CH\textsubscript{2})\textsubscript{r}-NR\textsuperscript{iii}R\textsuperscript{iv}, wherein

\[ r \text{ is } 1, 2 \text{ or } 3, \]

\[ R\textsuperscript{iii} \text{ and } R\textsuperscript{iv} \text{ is each individually selected from the group consisting of H and Cl\_6-alkyl, or } R\textsuperscript{iii} \text{ and } R\textsuperscript{iv} \text{ form together with the nitrogen to which they are attached a 3- to 7-membered heterocyclyl containing one or two heteroatoms individually selected from N, O and S, and which heterocyclyl is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of oxo, halogen, Cl\_6-alkyl and Cl\_6-alkoxy, and} \]

ix) -C(0)(CH\textsubscript{2})\textsubscript{s}-NR\textsuperscript{vi}R\textsuperscript{v}, wherein

\[ s \text{ is } 1, 2 \text{ or } 3, \]

\[ R\textsuperscript{v} \text{ and } R\textsuperscript{vi} \text{ is each individually selected from the group consisting of H and Cl\_6-alkyl, or } R\textsuperscript{v} \text{ and } R\textsuperscript{vi} \text{ form together with the nitrogen to which they are attached a 3- to 7-membered heterocyclyl containing one or two heteroatoms individually selected from N, O and S, and which heterocyclyl is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of oxo, halogen, C\textsubscript{1-6}-alkyl and Cl\_6-alkoxy;} \]

20 \[ R\textsuperscript{2} \text{ is halogen;} \text{ and} \]

\[ R\textsuperscript{3} \text{ is a 6-membered heteroaryl ring, unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of OH, halogen, cyano, Cl\_6-alkyl, Cl\_6-alkoxy, halogen-Cl\_6-alkyl, halogen-Cl\_6-alkoxy and hydroxy-Cl\_6-alkyl;} \]

or a pharmaceutically acceptable salt thereof.

25 A certain embodiment of the invention provides compounds of formula Ia,
where $R^1, R^2$ and $R^3$ are the same as described herein.

A certain embodiment of the invention provides compounds of formula I, where $R^1$ is selected from the group consisting of

i) $\text{H}$,

5 ii) $-\text{Ci}_6$-alkyl, unsubstituted or substituted by 1 to 2 substituents individually selected from the group consisting of halogen and $\text{Ci}_6$-alkoxy,

iii) $-\text{S(0)}_2$-$\text{Ci}_6$-alkyl, wherein the $\text{Ci}_6$-alkyl is unsubstituted,

iv) $-\text{C(0)}$-$\text{Ci}_6$-alkyl, wherein the $\text{Ci}_6$-alkyl is unsubstituted or substituted by 1 to 2 OH,

v) $-\text{C(0)}$0-$\text{Ci}_6$-alkyl, wherein the $\text{Ci}_6$-alkyl is unsubstituted;

vi) unsubstituted cycloalkyl,

vii) $\text{S(0)}_2$-$(\text{CH}_2)_q$-$\text{NR}^i\text{R}^{ii}$, wherein $q$ is 0,

$R^1$ and $R^{ii}$ is each individually selected from the group consisting of $\text{H}$ and $\text{Ci}_6$-alkyl,

viii) $(\text{CH}_2)_r$-$\text{NR}^{iii}\text{R}^{iv}$, wherein $r$ is 2,

$R^{iii}$ and $R^{iv}$ is each individually selected from the group consisting of $\text{H}$ and $\text{Ci}_6$-alkyl, and

ix) $-\text{C(0)}$(CH$_2$)$_s$-$\text{NR}^v$R$^{vi}$, wherein $s$ is 1,

$R^v$ and $R^{vi}$ is each individually selected from the group consisting of $\text{H}$ and $\text{Ci}_6$-alkyl.

A certain embodiment of the invention provides compounds of formula I, where $R^1$ is selected from the group consisting of

i) $\text{H}$,

20 ii) $-\text{Ci}_6$-alkyl, unsubstituted or substituted by 1 to 2 substituents individually selected from the group consisting of halogen and $\text{Ci}_6$-alkoxy, and

iii) unsubstituted cycloalkyl.

A certain embodiment of the invention provides compounds of formula I, where $R^1$ is selected from the group consisting of $\text{H}$, methyl, ethyl, isopropyl, 2,2-difluoroethyl, 2-methoxy-ethyl and cyclobutyl.
A certain embodiment of the invention provides compounds of formula I, where R1 is selected from the group consisting of Boc, H, methyl, ethyl, isopropyl, cyclobutyl, 2,2-difluoroethyl, 2-methoxyethyl, 2-methylaminoethyl, 1-oxo-ethyl, 1-oxo-2-hydroxy-ethyl, 1-oxo-2-dimethylamino-ethyl, methylsulfonyl and N,N-dimethylsulfonamidyl.

A certain embodiment of the invention provides compounds of formula I, where R1 is Boc.

A certain embodiment of the invention provides compounds of formula I, where R1 is H.

A certain embodiment of the invention provides compounds of formula I, where R1 is -C6-alkyl.

A certain embodiment of the invention provides compounds of formula I, where R1 is methyl.

A certain embodiment of the invention provides compounds of formula I, where R1 is ethyl.

A certain embodiment of the invention provides compounds of formula I, where R1 is isopropyl.

A certain embodiment of the invention provides compounds of formula I, where R1 is cycloalkyl.

A certain embodiment of the invention provides compounds of formula I, where R1 is cyclobutyl.

A certain embodiment of the invention provides compounds of formula I, where R1 is -C6-alkyl, substituted by 2 halogens.

A certain embodiment of the invention provides compounds of formula I, where R1 is 2,2-difluoroethyl.

A certain embodiment of the invention provides compounds of formula I, where R1 is -C6-alkyl, substituted by C6-alkoxy.

A certain embodiment of the invention provides compounds of formula I, where R1 is 2-methoxyethyl.

A certain embodiment of the invention provides compounds of formula I, where R1 is -(CH2)2NR111R111, wherein r is 2, and R111 and R111 are each individually selected from the group consisting of H and C6-alkyl.

A certain embodiment of the invention provides compounds of formula I, where R1 is 2-methylaminoethyl.
A certain embodiment of the invention provides compounds of formula I, where \( R^1 \) is -C(0)-Ci_6-alkyl, wherein the Ci_6-alkyl is unsubstituted or substituted by 1 to 2 OH

A certain embodiment of the invention provides compounds of formula I, where \( R^1 \) is 1-oxo-ethyl.

5 A certain embodiment of the invention provides compounds of formula I, where \( R^1 \) is 1-oxo-2-hydroxy-ethyl.

A certain embodiment of the invention provides compounds of formula I, where \( R^1 \) is \( \text{S}(0)\text{C}_1\text{C}_6-\text{alkyl} \).

10 A certain embodiment of the invention provides compounds of formula I, where \( R^1 \) is methylsulfonyl.

A certain embodiment of the invention provides compounds of formula I, where \( R^1 \) is \( \text{S}(0)\text{C}_1\text{C}_6-\text{alkyl} \).

15 A certain embodiment of the invention provides compounds of formula I, where \( R^1 \) is unsubstituted pyridazinyl, and

A certain embodiment of the invention provides compounds of formula I, where \( R^1 \) is selected from the group consisting of

i) pyridinyl, unsubstituted or substituted by 1 to 2 substituents individually selected from the group consisting of halogen, Ci_6-alkyl and Ci_6-alkoxy,

ii) pyrazinyl, unsubstituted or substituted by 1 to Ci_6-alkyl,

iii) unsubstituted pyridazinyl, and
iv) pyrimidinyl, unsubstituted or substituted by 1 to 2 Ci_6-alkyl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is

i) pyridinyl, unsubstituted or substituted by 1 to 2 substituents individually selected from the group consisting of halogen and Ci_6-alkyl, or

ii) unsubstituted pyrazinyl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is selected from the group consisting of pyridin-2-yl, 6-methyl-pyridin-2-yl, 3-chloro-pyridin-2-yl, 3,5-difluoro-pyridin-2-yl, 6-chloro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 3-fluoro-pyridin-2-yl and pyrazin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is pyridinyl, unsubstituted or substituted by 1 to 2 substituents individually selected from the group consisting of halogen, Ci_6-alkyl and Ci_6-alkoxy.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 6-methyl-pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 6-ethyl-pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 6-isopropyl-pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 6-methoxy-pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 3-chloro-pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 6-chloro-pyridin-2-yl.
A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 6-fluoro-pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 5-fluoro-pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 4-chloro-pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 3-fluoro-pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 3,5-difluoro-pyridin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is pyridin-3-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 2-chloro-pyridin-3-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is pyrazinyl, unsubstituted or substituted by 1 to 2 Ci_6-alkyl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is pyrazin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 6-methyl-pyrazin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is methyl-pyrazin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 3,6-dimethyl-pyrazin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is pyridazinyl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is pyridazin-3-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is pyrimidinyl, unsubstituted or substituted by 1 to 2 Ci_6-alkyl.
A certain embodiment of the invention provides compounds of formula I, where $R^3$ is pyrimidin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 4,6-dimethyl-pyrimidin-2-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is 2-methyl-pyrimidin-4-yl.

A certain embodiment of the invention provides compounds of formula I, where $R^3$ is selected from the group consisting of pyridin-2-yl, 6-methyl-pyridin-2-yl, 6-ethyl-pyridin-2-yl, 6-isopropyl-pyridin-2-yl, 6-methoxy-pyridin-2-yl, 6-chloro-pyridin-2-yl, 6-fluoro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 4-chloro-pyridin-2-yl, 3-fluoro-pyridin-2-yl, pyridin-3-yl, 2-chloro-pyridin-3-yl, 2-fluoro-pyridin-3-yl, pyrimidin-2-yl, 4,6-dimethyl-pyrimidin-2-yl, 2-methylpyrimidin-4-yl, pyrazin-2-yl, 6-methyl-pyrazin-2-yl, 3-methyl-pyrazin-2-yl, 3,6-dimethylpyrazin-2-yl and pyridazin-3-yl.

Examples for the compound according to the invention are shown in the experimental part and the table below.

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Table 2: structures of selected examples

Specific compounds of the invention are shown in the examples. A certain embodiment of the invention relates to compounds selected from the group consisting of

- in 8-Chloro-l-(4-pyridin-2-yl-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester,
- 8-Chloro-l-(4-pyrimidin-2-yl-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester,
- in 8-Chloro-l-(4-pyrimidin-2-yl-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester,
- 8-Chloro-5-methyl-l-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
- in 8-Chloro-5-methyl-l-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
- l-(irara-8-chloro-l-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6H)-yl)ethanone,
- l-(irara-8-chloro-l-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6H)-yl)-2-hydroxyethanone,
- l-(irara-8-chloro-l-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6H)-yl)-2-(dimethylamino)ethanone formate,
- 2-(irara-8-chloro-l-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6H)-yl)-N-methylethanamine,
in 8-Chloro-1-[4-(3,5-difluoro-pyridin-2-yl)-cyclohexyl]-4,6H-2,3,5,10b-tetraazabenzo[e]azulene-5-carboxylic acid tert-butyl ester,
in 8-Chloro-1-[4-(3,5-difluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraazabenzo[e]azulene,
in 8-Chloro-1-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraazabenzo[e]azulene,
in 8-Chloro-1-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraazabenzo[e]azulene-5-carboxylic acid tert-butyl ester,
in 8-chloro-1-(1R,4S)-4-(3-methylpyrazin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-chloro-1-((1R,4S)-4-(4-chloropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-chloro-1-((1R,4S)-4-(4-chloropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-chloro-1-((1R,4S)-4-(6-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-chloro-1-((1R,4S)-4-(6-fluoropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-1-(4-pyrazin-2-yl-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in 8-Chloro-1-(4-pyrazin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene dihydrochloride,
in 8-Chloro-1-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride,
in 8-Chloro-1-[4-(3,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride,
in 8-Chloro-1-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride,
in 8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,

trans-8-Chloro-1-[4-(4-pyridin-2-yl-cyclohexyl)]-5,6-dihydro-4H-2,3,5-1Ob-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in *ns*-8-Chloro-l-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4*H*-2,3,5,10b-tetraaza-benzoazulene dihydrochloride,
in *ns*-8-Chloro-l-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4*H*-2,3,5,10b-tetraaza-benzoazulene,
in *ns*-8-Chloro-l-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-4*H*-,6*H*-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in *ns*-8-Chloro-l-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4*H*-2,3,5,10b-tetraaza-benzo[e]azulene,
in *ns*-8-Chloro-l-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4*H*-2,3,5,10b-tetraaza-benzo[e]azulene,
in *ns*-8-Chloro-l-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-4*H*-,6*H*-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in *ns*-8-Chloro-l-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4*H*-2,3,5,10b-tetraaza-benzo[e]azulene,
in *ns*-8-Chloro-l-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4*H*-2,3,5,10b-tetraaza-benzo[e]azulene,
in *ns*-8-Chloro-l-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-4*H*-,6*H*-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in *ns*-8-Chloro-l-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4*H*-2,3,5,10b-tetraaza-benzo[e]azulene,
in *ns*-8-Chloro-l-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4*H*-2,3,5,10b-tetraaza-benzo[e]azulene,
in *ns*-8-Chloro-l-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-4*H*-,6*H*-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in *ns*-8-Chloro-l-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4*H*-2,3,5,10b-tetraaza-benzo[e]azulene,
in *ns*-8-Chloro-l-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4*H*-2,3,5,10b-tetraaza-benzo[e]azulene,
in *ns*-8-Chloro-l-[4-(6-methyl-pyrazin-2-yl)-cyclohexyl]-4*H*-,6*H*-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in *ns*-8-Chloro-l-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-4*H*-,6*H*-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in *ns*-8-chloro-5-(2,2-difluoroethyl)-l-((IR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4*H*-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in *ns*-8-chloro-5-cyclobutyl-1-((IR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4*H*-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-chloro-5-ethyl-1-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-chloro-5-methyl-1-((lR,4S)-4-(2-methylpyrimidin-4-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-chloro-5-methyl-1-((lR,4S)-4-(3-methylpyrazin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e]azulene,
in 8-Chloro-5-methyl-l-(4-pyrazin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-5-methyl-1-(4-pyridazin-3-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-5-methyl-l-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-5-methyl-l-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-5-methyl-l-[4-(6-methyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-5-methyl-l-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-fluoro-l-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-fluoro-l-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
trans-tert-butyl 8-chloro-l-((lR,4R)-4-(2-fluoropyridin-3-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6H)-carboxylate,
trans-tert-butyl 8-chloro-l-((lR,4S)-4-(2-chloropyridin-3-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6H)-carboxylate,
trans-tert-butyl 8-chloro-l-((lR,4S)-4-(2-methylpyrimidin-4-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6H)-carboxylate,
trans-tert-butyl 8-chloro-l-((lR,4S)-4-(3-methylpyrazin-2-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6H)-carboxylate,
trans-tert-butyl 8-chloro-l-((lR,4S)-4-(4-chloropyridin-2-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6H)-carboxylate,
trans-tert-butyl 8-chloro-l-((lR,4S)-4-(6-fluoropyridin-2-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6H)-carboxylate,
trans-tert-butyl 8-fluoro-l-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6H)-carboxylate,
or a pharmaceutically acceptable salt thereof.

A certain embodiment of the invention relates to compounds selected from the group consisting of
in ns-8-Chloro-l-(4-pyridin-2-yl-cyclohexyl)-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in ns-8-Chloro-l-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-5-methyl-l-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-l-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in ns-8-Chloro-l-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-5-methyl-l-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-l-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in ns-8-Chloro-l-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-l-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in ns-8-Chloro-l-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-l-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-l-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-4 H.6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
in ns-8-Chloro-l-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzoazulene,
in ns-8-Chloro-l-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzoazulene,
in ns-8-Chloro-l-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in ns-8-Chloro-l-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-l-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H.2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-l-(4-(6-fluoropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-l-[4-(5-fluoro-pyridin-2-yl)cyclohexyl]-4 _H_6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
in 8-Chloro-l-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 _H_-2,3,5,10b-tetraaza-benzoazulene,
trans-tert-Butyl 8-chloro-l-(4-(4-chloropyridin-2-yl)cyclohexyl)-4 _H_-benzo[e] [1,2,4]triazolo[4,3-a][1,4]diazepine-5(6 _H_)-carboxylate,
in 8-Chloro-l-(4-(4-chloropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-l-(4-(4-chloropyridin-2-yl)-cyclohexyl)-5-methyl-5,6-dihydro-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-l-[4-(3-fluoropyridin-2-yl)-cyclohexyl]-4 _H_6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in 8-Chloro-l-[4-(3-fluoropyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 _H_-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-l-[4-(3-fluoropyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 _H_-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-l-5-ethyl-l-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-l-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5-isopropyl-5,6-dihydro-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-l-5-cyclobutyl-l-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-l-5-(2,2-difluoroethyl)-l-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
iraw5’-8-Chloro-l-[4-(3-fluoropyridin-2-yl)-cyclohexyl]-5-(2-methoxyethyl)-5,6-dihydro-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
2-(iraw5’-8-Chloro-l-(-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 _H_)-yl)-N-methylethanamine,
1-(iraw5’-8-Chloro-l-(-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 _H_)-yl)ethanone,
1-(iraw5’-8-Chloro-l-(-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 _H_)-yl)-2-hydroxyethanone,
1-(iraw5’-8-Chloro-l-(-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 _H_-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 _H_)-yl)-2-(dimethylamino)ethanone,
in $ns$-8-Chloro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-N,N-dimethyl-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6 $H$)-sulfonamide,

$trans$-$tert$-Butyl 8-fluoro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6$H$)-carboxylate,

in $ns$-8-Fluoro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

in $ns$-8-Fluoro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

cis-$tert$-Butyl 8-fluoro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6$H$)-carboxylate,

cis$5'$-8-Fluoro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

in $ns$-8-Fluoro-1-(4-pyridin-3-yl-cyclohexyl)-4 $H.6H$-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid $tert$-butyl ester,

in $ns$-8-Chloro-1-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4 $H$-2,3,5,10b-tetraaza-benzo[e]azulene,

in $ns$-8-Chloro-5-methyl-1-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4 $H$-2,3,5,10b-tetraaza-benzo[e]azulene,

$trans$-$tert$-Butyl 8-chloro-1-(4-(2-chloropyridin-3-yl)cyclohexyl)-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6 $H$)-carboxylate,

in $ns$-8-Chloro-1-(4-(2-chloropyridin-3-yl)cyclohexyl)-5,6-dihydro-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

in $ns$-8-Chloro-1-(4-(2-chloropyridin-3-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

$trans$-$tert$-Butyl 8-chloro-1-(4-(2-fluoropyridin-3-yl)cyclohexyl)-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6$H$)-carboxylate,

in $ns$-8-Chloro-1-(4-(2-fluoropyridin-3-yl)cyclohexyl)-5,6-dihydro-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

in $ns$-8-Chloro-1-(4-(2-fluoropyridin-3-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 $H$-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

in $ns$-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-4 $H.6H$-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid $tert$-butyl ester,
d5'-8-Chloro-l-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene,
cis-8-Chloro-5-methyl-l-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in ns-8-Chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene.
A certain embodiment of the invention relates to compounds selected from the group consisting of:

- 8-Chloro-5-methyl-1-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene, dihydrochloride,
- 8-Chloro-5-methyl-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene, dihydrochloride,
- 8-Chloro-5-methyl-1-(4-(3-chloro-pyridin-2-yl)-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
- 8-Chloro-5-(2,2-difluoroethyl)-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
- 8-Chloro-5-(2-methoxyethyl)-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
- 8-Chloro-5-ethyl-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
A certain embodiment of the invention relates to compounds selected from the group consisting of

- 8-Chloro-1-[4-(3,5-difluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-5-methyl-1-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-1-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-1-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-5-ethyl-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5-isopropyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-5-cyclobutyl-1-(4-(3-fluoro-pyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-5-(2,2-difluoroethyl)-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.
- 8-Chloro-5-methyl-1-(4-pyrazin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.

A certain embodiment of the invention is a compound as described in any of the embodiments obtainable by a process according as described herein.
A certain embodiment of the invention is a compound as described in any of the embodiments, whenever obtained by a process according as described herein.

A certain embodiment of the invention is a compound as described in any of the embodiments for the use as therapeutically active substance.

A certain embodiment of the invention is a compound as described in any of the embodiments for a use in the prevention or treatment of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

A certain embodiment of the invention is a pharmaceutical composition comprising a compound as described in any of the embodiments.

A certain embodiment of the invention is a pharmaceutical composition comprising a compound as described in any of the embodiments, wherein it is useful for the prevention or treatment of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

A certain embodiment of the invention is the use of a compound as described in any of the embodiments for the preparation of a medicament.

A certain embodiment of the invention is the use of a compound as described in any of the embodiments for the preparation of a medicament, wherein the medicament is useful for the prevention or treatment of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

A certain embodiment of the invention is the use of a compound as described in any of the embodiments for the prevention or treatment of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

A certain embodiment of the invention is a method for the therapeutic and/or prophylactic treatment of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders,
schizophrenia, and aggressive behavior, which method comprises administering a compound as defined in any of the embodiments to a human being or animal.

In a certain embodiment, the compounds of formula I of the invention can be manufactured according to a process comprising the step of reacting a compound of formula II

\[
\begin{align*}
\text{II} & \\
\text{III} & \\
\text{I} & \text{n-butanol reflux}
\end{align*}
\]

with a compound of formula III,

\[
\begin{align*}
\text{II} & \\
\text{III} & \\
\text{I} & \text{n-butanol reflux}
\end{align*}
\]

to obtain a compound of formula I wherein \(R^1, R^2\) and \(R^3\) are as defined hereinabove for formula I.

The processes are described in more detail with the following general schemes and procedures A to G.

Scheme 1: General Scheme A

Compounds of formula I can be prepared by thermal condensation of a hydrazide of formula II and a thiolactam of formula III. The synthesis of compounds of formula II is outlined in general schemes D-G hereinafter. Compounds of formula III can be prepared following the procedures described in general scheme C as described hereinafter. General scheme A is hereinafter further illustrated with general procedure X.
Scheme 2: General Scheme B

Compounds of formula I with $R^1$ different from H can be prepared from compounds of formula 1-2 (compounds of formula I wherein $R^1$ is H) according to methods known in the art, e.g. by treating a compound of formula 1-2 with an inorganic base such as a carbonate salt or an organic base such as a tertiary amine and an electrophilic reactant $R^1$-LG (wherein LG is a leaving group like, halogen or sulfonyl) which is either commercially available or easily prepared according to methods and starting materials well known in the art. Alternatively, compounds of formula I can be obtained via reductive alkylation by consecutively treating a compound of formula 1-2 with a ketone or aldehyde and a suitable reducing agent like a borohydride derivative such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. Alternatively, compounds of formula I, in which $R^1$ is an acyl group, can be manufactured by coupling an amine of formula 1-2 with a carboxylic acid. The usual reagents and protocols known in the art can be used to effect the amide coupling. Compounds of formula 1-2 can be obtained by cleavage of the substituent $R^1$ of a compound of formula I using methods known in the art. Compounds of formula 1-2 are conveniently obtained as the salt or the free base after basic aqueous work-up by treatment of compounds of formula I-1 (compounds of formula I in which $R^1$ is iert-butoxycarbonyl) with an acid in a suitable solvent like methanesulphonic acid in dichloromethane or tetrahydrofuran or hydrochloric acid in methanol. General scheme B is hereinafter further illustrated with general procedures XI and XII.
Scheme 3: General Scheme C

A thiolactam of formula III-1 (compounds of formula III in which R1 is tert-butoxycarbonyl) can be obtained as follows: Transformation of a 2-nitrobenzyl alcohol of formula a to a benylic chloride of formula b can be affected by a chlorinating reagent such as thionyl chloride in the presence of an organic tertiary amine base. Alkylation of a compound of formula b with glycine ethyl ester hydrochloride in the presence of an organic tertiary amine base and N-protection of the resulting compound of formula c using di-tert-butyl dicarbonate and a catalytic amount of 4-N,N-dimethylaminopyridine gives compounds of formula d. The nitro group can be reduced selectively by hydrogenation over palladium or platinum on charcoal, which has been pretreated with a zinc halide such as zinc bromide, to give aniline intermediates of formula e. Cyclization to lactams of formula f is achieved by treatment of compounds of formula e with a suitable base, e.g. potassium tert-butoxide, in tetrahydrofuran. A thiolactam of formula III-1 is obtained by treatment of a compound of formula f with Lawesson's reagent or phosphorous pentasulphide at elevated temperature.
Scheme 4: General Scheme D

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester intermediates of formula V can be prepared under the conditions of the Suzuki reaction from a 4-trifluoromethanesulfonyloxy-cyclohex-3-enecarboxylic acid ester of formula IV and a heteroaryl boronic acid, a heteroaryl boronic acid ester or a heteroaryl trifluoroborate salt in a suitable organic solvent such as 1,4-dioxane, 1,2-dimethoxyethane, tetrahydrofuran or toluene in the presence of catalytic amounts of a 1:2 mixture of palladium(II) acetate and triphenylphosphine or a 1:1 mixture of palladium(II) acetate and a bisphosphine ligand or tetrakis(triphenylphosphine)palladium(0) and in the
presence of a base such as an alkali metal salt of phosphate or carbonate, which is used neat or as an aqueous solution, at a reaction temperature between room temperature and reflux. Alternatively 4-heteroaryl-cyclohex-3-enecarboxylic acid ester intermediates of formula V can be prepared under the conditions of the Negishi reaction from a 4-trifluoromethanesulfonyloxy-cyclohex-3-enecarboxylic acid ester of formula IV and a heteroaryl zinc halide in a suitable organic solvent such as tetrahydrofuran and Pd(PPh)$_3$ at a reaction temperature between room temperature and reflux. Alternatively compounds of formula V can be prepared by coupling a potassium trifluoroborate salt of formula VII with a heteroaryl halide R$^3$-X in the presence of a base such as potassium carbonate and a suitable palladium catalyst such as (1,3-disopropylimidazol-2-ylidene)(3-chloropyridyl)palladium (II) chloride in a suitable solvent such as an alcohol at reflux. A potassium trifluoroborate salt of formula VII can be prepared by treatment of an (RS)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-cyclohex-3-enecarboxylic acid ester of formula VI with potassium hydrogen difluoride in a mixture of acetone and water at room temperature. Compounds of formula VI can be obtained by coupling a compound of formula IV with bis(pinacolato)diboron in the presence of a suitable base such as potassium acetate and a suitable palladium catalyst such as a 1:1 mixture of 1,1'-bis(diphenylphosphino)ferrocene and dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloromethane adduct in a suitable solvent such as 1,4-dioxane at 90 °C. Compounds of formula V can alternatively be prepared under the conditions of the Suzuki reaction from a compound of formula VI and a heteroaryl halide R$^3$-X in a suitable organic solvent such as 1,4-dioxane, 1,2-dimethoxyethane, tetrahydrofuran or toluene in the presence of catalytic amounts of a 1:2 mixture of palladium(II) acetate and triphenylphosphine or a 1:1 mixture of palladium(II) acetate and a bisphosphine ligand or tetrakis(triphenylphosphine)palladium(0) and in the presence of a base such as an alkali metal salt of phosphate or carbonate, which is used neat or as an aqueous solution, at a reaction temperature between room temperature and reflux. General scheme D is hereinafter further illustrated with general procedures I to III.
4-Heteroaryl-cyclohexane carboxylic acid ester intermediates of formula VIII are usually obtained as a mixture of the *cis* and the *trans* isomer by reduction of 4-heteroaryl-cyclohex-3-enyl carboxylic acid ester intermediates of formula V under an atmosphere of hydrogen gas (1 bar) in a suitable solvent such as ethyl acetate or an alcohol in the presence of a catalytic amount of palladium or platinum on charcoal or platinum(IV) oxide at room temperature. Compounds of formula V and VIII, the residue R³ of which is substituted with one or more halide substituents other than fluorine may undergo partial or complete dehalogenation under these reaction conditions. The acid formed as a consequence of the dehalogenation reaction may be neutralized by addition of a base such as a trialkyl amine to the reaction mixture. Pretreatment of the palladium or platinum catalyst with a zinc halide may in some cases prevent or reduce dehalogenation of compounds of formula V and VIII, the residue R³ of which is substituted with one or more halide substituents other than fluorine. *Cis/trans* mixtures of 4-heteroaryl-cyclohexane carboxylic acid ester intermediates of formula VIII may in some cases be separable by the usual methods such as silica gel column or high performance chromatography or crystallization into pure *cis*-4-heteroaryl-cyclohexane carboxylic acid ester intermediates of formula VHI-a and in *cis*-4-heteroaryl-cyclohexane carboxylic acid ester intermediates of formula VHI-b, which can be saponified to pure *cis*-4-heteroaryl-cyclohexane carboxylic acid intermediates of formula IX-a and in *cis*-4-heteroaryl-cyclohexane carboxylic acid intermediates of formula IX-b under standard conditions such as stirring in a mixture of aqueous sodium hydroxide solution and an etheral solvent such as 1,4-dioxane, tetrahydrofuran or diethyl ether a
room temperature. Alternatively, in \( nS \)-4-heteroaryl-cyclohexane carboxylic acid intermediates of formula IX-b can be obtained by epimerization of the cis isomer of cis/trans-mixtures of 4-heteroaryl-cyclohexane carboxylic acid ester intermediates of formula VIII using a suitable base, e.g. an alkali metal alkoxide such as sodium or potassium methylete or ethylate, in a suitable solvent such as methanol, ethanol or toluene at reflux followed by saponification of the crude reaction mixture, which may consist of a mixture of a in \( nS \)-4-heteroaryl-cyclohexane carboxylic acid intermediate of formula IX-b and a in \( nS \)-4-heteroaryl-cyclohexane carboxylic acid ester intermediate of formula VHI-b, under standard conditions such as stirring in a mixture of aqueous sodium hydroxide solution and an etheral solvent such as 1,4-dioxane, tetrahydrofuran or diethyl ether at room temperature. In case the epimerization reaction was carried out in an alcohol as solvent, the crude reaction mixture can alternatively be acidified by the addition of concentrated sulfuric acid and heated to reflux to obtain a in \( nS \)-4-heteroaryl-cyclohexane carboxylic acid ester intermediate of formula VHI-b. General scheme E is hereinafter further illustrated with general procedures IV to VII.

\[ \text{Scheme 6: General Scheme F} \]

Compounds of formula VIII-1 (compounds of formula VIII, in which \( R^{3} \) is a 2-chloropyridin-3-yl group) can be prepared from compounds of formula VIII-2 (compounds of formula VIII, in which \( R^{3} \) is a 2-amimo-pyridin-3-yl group) by consecutive treatment with a mixture of concentrated hydrochloric acid and sodium nitrite and copper(I) chloride. Compounds of formula VIII-2 can be converted to compounds of formula VIII-3 (compounds of formula VIII, in which...
R is a 2-fluoro-pyridin-3-yl group) and compounds of formula VIII-4 (compounds of formula VIII, in which R is a 6-amino-pyridin-2-yl group) can be converted to compounds of formula VIII-5 (compounds of formula VIII, in which R is a 6-fluoro-pyridin-2-yl group) by treatment with 70% HF-pyridine and sodium nitrite. Compounds of formula VIII-7 (compounds of formula VIII, in which R is a 6-chloro-pyridin-2-yl group) can be synthesized from compounds of formula VIII-6 (compounds of formula VIII, in which R is a 6-methoxy-pyridin-2-yl group) by treatment with phosphorus oxy chloride in N,N-dimethylformamide at 120 °C.

A 4-heteroaryl-cyclohexanecarboxylic acid ester intermediate of formula VIII can be converted to a hydrazide of formula II by heating with hydrazine hydrate. Alternatively, an ester of formula VIII can be hydrolyzed to a carboxylic acid of formula IX using a biphasic mixture of aqueous sodium or potassium hydroxide solution and an ethereal solvent such as dioxane, tetrahydrofuran or diethyl ether. A hydrazide of formula II can be obtained by activating an acid intermediate of formula IX, e.g. with ethyl chloroformate, thionyl chloride, oxalylchloride or a peptide coupling reagent, and subsequent coupling with hydrazine. General scheme G is hereinafter further illustrated with general procedures VII to IX.

The corresponding pharmaceutically acceptable salts with acids can be obtained by standard methods known to the person skilled in the art, e.g. by dissolving the compound of formula I in a suitable solvent such as e.g. dioxan or THF and adding an appropriate amount of the corresponding acid. The products can usually be isolated by filtration or by chromatography. The conversion of a compound of formula I into a pharmaceutically acceptable salt with a base can be carried out by treatment of such a compound with such a base. One possible method to
form such a salt is e.g. by addition of 1/n equivalents of a basic salt such as e.g. M(OH)$_n$, wherein M is metal or ammonium cation and n is number of hydroxide anions, to a solution of the compound in a suitable solvent (e.g. ethanol, ethanol-water mixture, tetrahydrofuran-water mixture) and to remove the solvent by evaporation or lyophilisation.

Insofar as their preparation is not described in the examples, the compounds of formula I as well as all intermediate products can be prepared according to analogous methods or according to the methods set forth herein. Starting materials are commercially available, known in the art or can be prepared by methods known in the art or in analogy thereto.

It will be appreciated that the compounds of formula I in this invention can be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

**Pharmacological Tests**

The compounds of the present invention exhibit Via activity. They are selective inhibitors of the Via receptor and are therefore likely to have a low potential to cause unwanted off-target related side-effects. The Via activity can be detected as described below.

The human Via receptor was cloned by RT-PCR from total human liver RNA. The coding sequence was subcloned in an expression vector after sequencing to confirm the identity of the amplified sequence. To demonstrate the affinity of the compounds from the present invention to the human Via receptor binding studies were performed. Cell membranes were prepared from HEK293 cells transiently infected with the expression vector and grown in 20 liter fermenters with the following protocol.

50g of cells are resuspended in 30 ml freshly prepared ice cold Lyses buffer (50mM HEPES, 1mM EDTA, 10mM magnesium dichloride adjusted to pH= 7.4 + complete cocktail of protease inhibitor (Roche Diagnostics)). Homogenized with Polytron for 1min and solicited on ice for 2x 2 minutes at 80% intensity (Vibrate solicitor). The preparation is centrifuged 20 min at 500 g at 4°C, the pellet is discarded and the supernatant centrifuged lhour at 43'000g at 4°C (19'000rpm). The pellet is resuspended in 12.5 ml Lyses buffer+12.5ml sucrose 20% and homogenized using a Polytron for 1-2 min. The protein concentration is determined by the Bradford method and aliquots are stored at -80°C until use. For binding studies 60mg Yttrium silicate SPA beads (Habersham®) are mixed with an aliquot of membrane in binding buffer (50 mM Tris, 120mM sodium chloride, 5 mM potassium chloride, 2 mM calcium dichloride, 10 mM magnesium dichloride) for 15 minutes with mixing. 50µl of bead/membrane mixture is then added to each well of a 96 well plate, followed by 50µl of 4 nM 3H-Vasopressin (American Radiolabeled Chemicals). For total binding measurement 100µl of binding buffer are added to the respective wells, for non-specific binding 100µl of 8.4mM cold vasopressin and for compound testing 100µl of a serial dilution of each compound in 2% dimethyl sulfoxide. The
plate is incubated 1h at room temperature, centrifuged 1 min at 1000g and counted on a Packard Top-Count. Non-specific binding counts are subtracted from each well and data is normalized to the maximum specific binding set at 100%. To calculate an IC₅₀ the curve is fitted using a non-linear regression model (XLfit) and the Ki is calculated using the Cheng-Prussoff equation.

The following representative data show the antagonistic activity against human Via receptor of compounds according to present invention.

<table>
<thead>
<tr>
<th>Ex#</th>
<th>pKi (hV1a)</th>
<th>Ex#</th>
<th>pKi (hV1a)</th>
<th>Ex#</th>
<th>pKi (hV1a)</th>
<th>Ex#</th>
<th>pKi (hV1a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>23</td>
<td>8.14</td>
<td>45</td>
<td>8.30</td>
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<td>9.00</td>
<td>46</td>
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<td>68</td>
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<td>9.37</td>
<td>47</td>
<td>7.60</td>
<td>69</td>
<td>9.22</td>
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<td>9.00</td>
<td>48</td>
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<td>70</td>
<td>7.82</td>
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<tr>
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<td>9.27</td>
<td>49</td>
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<td>71</td>
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<td>9.70</td>
<td>50</td>
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<td>8.66</td>
<td>73</td>
<td>7.26</td>
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<tr>
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<td>7.35</td>
<td>30</td>
<td>9.22</td>
<td>52</td>
<td>7.09</td>
<td>74</td>
<td>7.95</td>
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<tr>
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<td>8.96</td>
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<td>32</td>
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<td>54</td>
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<td>76</td>
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<td>55</td>
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<td>9.73</td>
<td>56</td>
<td>8.09</td>
<td>78</td>
<td>9.10</td>
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<tr>
<td>13</td>
<td>9.30</td>
<td>35</td>
<td>9.01</td>
<td>57</td>
<td>8.80</td>
<td>79</td>
<td>8.17</td>
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<tr>
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<td>7.25</td>
<td>36</td>
<td>7.55</td>
<td>58</td>
<td>7.69</td>
<td>80</td>
<td>8.14</td>
</tr>
<tr>
<td>15</td>
<td>8.48</td>
<td>37</td>
<td>8.79</td>
<td>59</td>
<td>8.03</td>
<td>81</td>
<td>8.33</td>
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<tr>
<td>16</td>
<td>9.52</td>
<td>38</td>
<td>8.64</td>
<td>60</td>
<td>8.66</td>
<td>82</td>
<td>9.30</td>
</tr>
<tr>
<td>17</td>
<td>8.55</td>
<td>39</td>
<td>8.60</td>
<td>61</td>
<td>6.37</td>
<td>83</td>
<td>8.14</td>
</tr>
<tr>
<td>18</td>
<td>9.22</td>
<td>40</td>
<td>9.75</td>
<td>62</td>
<td>7.02</td>
<td>84</td>
<td>9.30</td>
</tr>
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<td>19</td>
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<td>9.22</td>
<td>63</td>
<td>9.40</td>
<td>85</td>
<td>8.96</td>
</tr>
<tr>
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<td>7.78</td>
<td>42</td>
<td>9.28</td>
<td>64</td>
<td>7.73</td>
<td>86</td>
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<tr>
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<td>43</td>
<td>7.61</td>
<td>65</td>
<td>8.64</td>
<td>87</td>
<td>8.89</td>
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<tr>
<td>22</td>
<td>9.52</td>
<td>44</td>
<td>8.05</td>
<td>66</td>
<td>8.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: human Via pKi of selected examples
Pharmaceutical Compositions

The compounds of formula I as well as their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragees, hard and soft gelatin capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and their pharmaceutically acceptable salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatin capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragees and hard gelatin capsules. Suitable excipients for soft gelatin capsules are e.g. vegetable oils, waxes, fats, semisolid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc. Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc. Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

Examples of compositions according to the invention are, but are not limited to:

Example A

Tablets of the following composition are manufactured in the usual manner:
### Table 4: possible tablet composition

<table>
<thead>
<tr>
<th>ingredient</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>1. compound of formula I</td>
<td>5</td>
</tr>
<tr>
<td>2. lactose</td>
<td>45</td>
</tr>
<tr>
<td>3. corn starch</td>
<td>15</td>
</tr>
<tr>
<td>4. microcrystalline cellulose</td>
<td>34</td>
</tr>
<tr>
<td>5. magnesium stearate</td>
<td>1</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

### Manufacturing Procedure

1. Mix ingredients 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add ingredient 5 and mix for three minutes; compress on a suitable press.

### Example B-l

Capsules of the following composition are manufactured:

<table>
<thead>
<tr>
<th>ingredient</th>
<th>mg/capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>1. compound of formula I</td>
<td>5</td>
</tr>
<tr>
<td>2. lactose</td>
<td>159</td>
</tr>
<tr>
<td>3. corn starch</td>
<td>25</td>
</tr>
<tr>
<td>4. talc</td>
<td>10</td>
</tr>
<tr>
<td>5. magnesium stearate</td>
<td>1</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>200</strong></td>
</tr>
</tbody>
</table>

### Table 5: possible capsule ingredient composition

**Manufacturing Procedure**
1. Mix ingredients 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add ingredients 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

The compound of formula I, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc (and magnesium stearate) is added thereto and mixed thoroughly. The mixture is filled by machine into suitable capsules, e.g. hard gelatin capsules.

Example B-2

Soft Gelatin Capsules of the following composition are manufactured:

<table>
<thead>
<tr>
<th>ingredient</th>
<th>mg/capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of formula I</td>
<td>5</td>
</tr>
<tr>
<td>yellow wax</td>
<td>8</td>
</tr>
<tr>
<td>hydrogenated soybean oil</td>
<td>8</td>
</tr>
<tr>
<td>partially hydrogenated plant oils</td>
<td>34</td>
</tr>
<tr>
<td>soybean oil</td>
<td>110</td>
</tr>
<tr>
<td>total</td>
<td>165</td>
</tr>
</tbody>
</table>

Table 6: possible soft gelatin capsule ingredient composition

<table>
<thead>
<tr>
<th>ingredient</th>
<th>mg/capsule</th>
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</thead>
<tbody>
<tr>
<td>gelatin</td>
<td>75</td>
</tr>
<tr>
<td>glycerol 85 %</td>
<td>32</td>
</tr>
<tr>
<td>karion 83</td>
<td>8 (dry matter)</td>
</tr>
<tr>
<td>titanium dioxide</td>
<td>0.4</td>
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<tr>
<td>iron oxide yellow</td>
<td>1.1</td>
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<tr>
<td>total</td>
<td>116.5</td>
</tr>
</tbody>
</table>

Table 7: possible soft gelatin capsule composition
Manufacturing Procedure

The compound of formula I is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

5 Example C

Suppositories of the following composition are manufactured:

<table>
<thead>
<tr>
<th>ingredient</th>
<th>mg/supp.</th>
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</thead>
<tbody>
<tr>
<td>compound of formula I</td>
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</tr>
<tr>
<td>suppository mass</td>
<td>1285</td>
</tr>
<tr>
<td>total</td>
<td>1300</td>
</tr>
</tbody>
</table>

Table 8: possible suppository composition

Manufacturing Procedure

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered compound of formula I is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool; the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

Example D

15 Injection solutions of the following composition are manufactured:

<table>
<thead>
<tr>
<th>ingredient</th>
<th>mg/injection solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of formula I</td>
<td>3</td>
</tr>
<tr>
<td>polyethylene Glycol 400</td>
<td>150</td>
</tr>
<tr>
<td>acetic acid</td>
<td>q.s. ad pH 5.0</td>
</tr>
<tr>
<td>water for injection solutions</td>
<td>ad 1.0 ml</td>
</tr>
</tbody>
</table>

Table 9: possible injection solution composition
Manufacturing Procedure

The compound of formula I is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by acetic acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example E

Sachets of the following composition are manufactured:

<table>
<thead>
<tr>
<th>ingredient</th>
<th>mg/sachet</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of formula I</td>
<td>50</td>
</tr>
<tr>
<td>lactose, fine powder</td>
<td>1015</td>
</tr>
<tr>
<td>microcrystalline cellulose (AVICEL PH 102)</td>
<td>1400</td>
</tr>
<tr>
<td>sodium carboxymethyl cellulose</td>
<td>14</td>
</tr>
<tr>
<td>polyvinylpyrrolidone K 30</td>
<td>10</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>10</td>
</tr>
<tr>
<td>flavoring additives</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>2500</td>
</tr>
</tbody>
</table>

Table 10: possible sachet composition

Manufacturing Procedure

The compound of formula I is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidone in water. The granulate is mixed with magnesium stearate and the flavoring additives and filled into sachets.

Examples

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.
Intermediate of formula IV

(RS)-4-Trifluoromethanesulfonyloxy-cyclohex-3-enecarboxylic acid ethyl ester

To a solution of ethyl-4-cyclohexanonecarboxylate (25.0 g, 147 mmol) in tetrahydrofuran (580 ml) was added a 1M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (154 ml, 154 mmol) at -78 °C. Stirring for 1 h was followed by addition of a solution of N-phenyl-bis(trifluoromethanesulfonylimide) (55.1 g, 154 mmol) in tetrahydrofuran (80 ml). The cooling bath was removed 30 minutes after completed addition, and the reaction mixture was stirred for 12 h at room temperature. The mixture was quenched with 1 M aqueous sodium hydrogen sulfate solution (154 ml, 154 mmol). The solvent was removed by rotary evaporation (water bath of 40 °C). The residue was partitioned between iert-butyl methyl ether (500 ml) and 0.5 M aqueous sodium hydroxide solution (400 ml). The organic layer was washed with two 400-ml portions of 0.5 M aqueous sodium hydroxide solution, one 200-ml portion of saturated ammonium chloride solution and one 100-ml portion of brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give the title compound (41.8 g, 94.2%) as yellow oil, which was used in the following steps without further purification. MS m/e: 273 ([M-C\textsubscript{2}H\textsubscript{5}]\textsuperscript{+}).

Intermediate of formula (VI)

(RS)-4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

A mixture of (RS)-4-trifluoromethanesulfonyloxy-cyclohex-3-enecarboxylic acid ethyl ester (3.0 g, 9.92 mmol), potassium acetate (2.92 g, 29.8 mmol) and bis(pinacolato)diboron (3.78 g, 14.9 mmol) in 1,4-dioxane (30 ml) was purged with argon. Addition of 1,1'-bis(diphenylphosphino)ferrocene (0.17 g, 0.30 mmol) and dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloromethane adduct (0.22 g, 0.30 mmol) was followed by stirring at 90 °C for 18 h. The reaction mixture was partitioned between ethyl acetate (200 ml) and water (150 ml). The layers were separated. The organic layer was washed with one portion of brine, dried over anhydrous sodium sulfate and concentrated to dryness.
Flash-chromatography with n-heptane/ethyl acetate as eluent gave the title compound (1.95 g, 70%) as light yellow oil. MS m/e: 281 ([M+H]+)

Intermediate of formula (VII)

Potassium (RS)-(4-(ethoxycarbonyl)cyclohex-1-enyl)trifluoroborate

\[
\text{O} \quad \text{BF}_3^- \quad \text{K}^+ \\
\text{O}
\]

To a solution of (RS)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester (0.37 g, 1.32 mmol) in acetone (9 ml) and water (3 ml) was added potassium hydrogen difluoride (0.41 g, 5.28 mmol). Stirring for 4 h at room temperature was followed by evaporation of the solvent mixture. The residue was triturated in warm acetonitrile (20 ml). The solids were removed by filtration. The filtrate was concentrated to dryness to give the title compound (0.35 g, quantitative) as white solid which was used without further purification in the next step.

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester intermediates of formula (V)

General procedure (I):

A mixture of (RS)-4-trifluoromethanesulfonxyloxy-cyclohex-3-enecarboxylic acid ethyl ester (1 eq), a heteroaryl zinc halide (1-1.2 eq) and tetrakis(triphenylphosphine)palladium (0.05 eq) in dry tetrahydrofuran (0.3 M) is stirred at reflux for 14-20 h. After cooling to room temperature the reaction mixture is partitioned between an organic solvent such as tert-butyl methyl ether or ethyl acetate and water. The layers are separated. The aqueous layer is extracted with two or three portions of organic solvent. The combined organic layers are dried over anhydrous sodium sulfate and concentrated to dryness. Purification by flash-chromatography gives a 4-heteroaryl-cyclohex-3-enecarboxylic acid ester intermediate of formula (V).

General procedure (II):

A mixture of (RS)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester (1 eq) and a heteroaryl halide (1.3 eq) in a 4:1 mixture of 1,2-dimethoxyethane and 2M aqueous sodium carbonate solution (0.3 M) is purged with argon. After consecutive addition of triphenylphosphine (0.1 eq) and palladium(II)acetate (0.05 eq) the mixture is stirred at 80 °C for 20 h. After cooling to room temperature the reaction mixture is partitioned between an organic solvent such as tert-butyl methyl ether or ethyl acetate and water. The layers are separated. The aqueous layer is extracted with two or three portions of organic solvent. The combined organic layers are dried over anhydrous sodium sulfate and concentrated to dryness.
Purification by flash-chromatography gives a 4-heteroaryl-cyclohex-3-enecarboxylic acid ester intermediate of formula (V).

**General procedure (III):**

To a mixture of potassium (RS)-(4-(ethoxycarbonyl)cyclohex-1-enyl)trifluoroborate (1 eq), a heteroaryl halide (1.2 eq) and potassium carbonate (3 eq) in an alcohol such as ethanol or methanol (0.2 M) is added (1,3-diisopropylimidazol-2-ylidene)(3-chloropyridyl)palladium (II) chloride (0.02 eq). The mixture is stirred at reflux for 1-20 h. After cooling to room temperature the solvent is evaporated. The residue is triturated in an organic solvent such as tert-butyl methyl ether or ethyl acetate. The precipitates are removed by filtration. The filtrate is concentrated to dryness. Purification by flash-chromatography gives a 4-heteroaryl-cyclohex-3-enecarboxylic acid ester intermediate of formula (V).

**4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 1**

(RS)-4-Pyridin-2-yl-cyclohex-3-enecarboxylic acid ethyl ester

![Chemical structure of 4-Pyridin-2-yl-cyclohex-3-enecarboxylic acid ethyl ester](image)

The title compound was obtained as colorless oil in 63% yield from 2-pyridylzinc bromide according to general procedure (I). MS m/e: 232 ([M+H]+)

**4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 2**

(RS)-4-(6-Methyl-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

![Chemical structure of 4-(6-Methyl-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester](image)

The title compound was obtained as colorless liquid in 56% yield from 2-methyl-6-pyridylzinc bromide according to general procedure (I). MS m/e: 246 ([M+H]+)
4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 3

(RS)-4-(6-Ethyl-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

![Chemical Structure]

The title compound was obtained as yellow oil in 35% yield from 2-ethyl-6-pyridylzinc chloride according to general procedure (I). MS m/e: 260 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 4

(RS)-4-(6-Isopropyl-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

![Chemical Structure]

The title compound was obtained as yellow liquid in 55% yield from 2-isopropyl-6-pyridylzinc chloride according to general procedure (I). MS m/e: 274 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 5

(RS)-4-(6-Methoxy-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

![Chemical Structure]
The title compound was obtained as light yellow liquid in 86% yield from 2-bromo-6-methoxypyridine according to general procedure (III). MS m/e: 262 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 6

(RS)-4-(6-Amino-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

![Structure](image)

The title compound was obtained as light yellow liquid in 86% yield from 2-bromo-6-aminopyridine according to general procedure (III). MS m/e: 247 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 7

(RS)-4-(5-Fluoro-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

![Structure](image)

The title compound was obtained as colorless oil in 86% yield from 2-bromo-5-fluoropyridine according to general procedure (III). MS m/e: 250 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 8

(RS)-4-(4-Amino-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester
The title compound was obtained as light yellow oil in 40% yield from 2-chloro-4-aminopyridine according to general procedure (III). MS m/e: 247 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 9

(RS)-4-(3-Fluoro-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

The title compound was obtained as colorless oil in 89% yield from 2-bromo-3-fluoropyridine according to general procedure (III). MS m/e: 250 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 10

(RS)-4-Pyridin-3-yl-cyclohex-3-enecarboxylic acid ethyl ester

The title compound was obtained as colorless oil in 82% yield from 3-bromopyridine according to general procedure (III). MS m/e: 232 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 11

(RS)-4-(2-Amino-pyridin-3-yl)-cyclohex-3-enecarboxylic acid ethyl ester
The title compound was obtained as colorless oil in 60% yield from 2-amino-3-bromopyridine according to general procedure (III). MS m/e: 247 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 12

(RS)-4-Pyrimidin-2-yl-cyclohex-3-enecarboxylic acid ethyl ester

The title compound was obtained as light yellow oil in 47% yield from 3-bromopyrimidine according to general procedure (II). MS m/e: 233 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 13

(RS)-4-(4,6-Dimethyl-pyrimidin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

The title compound was obtained as white solid in 65% yield from 2-chloro-4,6-dimethylpyrimidine according to general procedure (III). MS m/e: 261 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 14

(RS)-4-(2-Methyl-pyrimidin-4-yl)-cyclohex-3-enecarboxylic acid ethyl ester
The title compound was obtained as colorless oil in 52% yield from 4-chloro-2-methylpyrimidine according to general procedure (III). MS m/e: 247 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 15

(RS)-4-(3-Chloro-pyrazin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

The title compound was obtained as colorless oil in 52% yield from 2,3-dichloropyrazine according to general procedure (III). MS m/e: 267 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 16

(RS)-4-(6-Methyl-pyrazin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

The title compound was obtained as yellow oil in 73% yield from 2-chloro-6-methylpyrazine according to general procedure (III). MS m/e: 247 ([M+H]+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 17

(RS)-4-(3-Methyl-pyrazin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester
The title compound was obtained as light yellow oil in 41% yield from 2-chloro-3-methylpyrazine according to general procedure (III). MS m/e: 247 ([M+H]+)

**4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 18**

(RS)-4-(3,6-Dimethyl-pyrazin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

The title compound was obtained as yellow oil in 76% yield from 2-chloro-3,6-dimethylpyrazine according to general procedure (III). MS m/e: 261 ([M+H]+)

**4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 19**

(RS)-4-(6-Chloro-pyridazin-3-yl)-cyclohex-3-enecarboxylic acid ethyl ester

The title compound was obtained as light brown solid in 64% yield from 3,6-dichloropyridazine according to general procedure (III).

MS m/e: 267 ([M+H]+)
4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 20

(RS)-4-(3-Amino-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

The title compound was obtained as light yellow solid in 65% yield from 3-amino-2-chloropyridine according to general procedure (III). MS m/e: 247 ([M+H]^+)

4-Heteroaryl-cyclohex-3-enecarboxylic acid ester 21

(RS)-4-(3,5-Difluoro-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester

The title compound was obtained as colorless oil in 61% yield from 2-bromo-3,5-difluoropyridine according to general procedure (III). MS m/e: 268 ([M+H]^+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediates of formula (VIII)

**General procedure (IV):** Platinum(IV)oxide catalyzed hydrogenation

A solution of a 4-heteroaryl-cyclohex-3-enecarboxylic acid ester intermediate of formula V in ethyl acetate (0.1 M) is purged with argon. Addition of platinum(IV) oxide (0.3 eq) is followed by filling the flask with hydrogen. The reaction mixture is stirred at room temperature under an atmosphere of hydrogen (1 bar) for 1-16 h. The catalyst is removed by filtration over Decalite®. The filtrate is concentrated to dryness to give a cis/trans mixture of a crude 4-heteroaryl-cyclohexanecarboxylic acid ester intermediate of formula VIII, which can usually be used in the next step without further purification.

**General procedure (V):** Palladium on charcoal catalyzed hydrogenation


A solution of a 4-heteroaryl-cyclohex-3-enecarboxylic acid ester intermediate of formula V and optionally a base such as triethylamine (1 eq) in an organic solvent such as ethyl acetate or toluene (0.1 M) is purged with argon. Addition of 10% palladium on activated charcoal (0.05 eq) is followed by filling the flask with hydrogen. The reaction mixture is stirred at room temperature under an atmosphere of hydrogen (1 bar) for 20-72 h. The catalyst is removed by filtration over Decalite®. The filtrate is washed with one portion of water. The aqueous layer is extracted with one or two portions of ethyl acetate. The combined organic layers are dried over anhydrous sodium sulfate and concentrated to dryness to give a cis/trans mixture of a crude 4-heteroaryl-cyclohexanecarboxylic acid ester intermediate of formula VIII, which can usually be used in the next step without further purification.

**General procedure (VI): Epimerization**

A mixture of ds/Zraws^+\-heteroaryl-cyclohexanecarboxylic acid ester intermediate of formula VIII and sodium ethylate (3-6 eq) in ethanol is heated at reflux for 20-72 h. Under these reaction conditions partial saponification of the resulting in \(n_5\)-4-heteroaryl-cyclohexanecarboxylic acid ester intermediate of formula VIII-b to a in \(n_5\)-4-heteroaryl-cyclohexanecarboxylic acid intermediate of formula IX-b may occur. Such a in \(n_5\)-4-heteroaryl-cyclohexanecarboxylic acid intermediate of formula IX-b can be reconverted to a in \(n_5\)-4-heteroaryl-cyclohexanecarboxylic acid ester intermediate of formula VIII-b by consecutive cooling of the mixture to 0-5 °C, addition of concentrated sulfuric acid (7-9 eq) and heating of the mixture at reflux for 1-2 h. After cooling to room temperature the reaction mixture is partitioned between an organic solvent such as ethyl acetate or tert-butyl methyl ether and 2M aqueous sodium carbonate solution. The layers are separated. The aqueous layer is extracted with two or three portions of organic solvent. The combined organic layers are dried over anhydrous sodium sulfate and concentrated to dryness. Purification by flash-chromatography gives a in \(n_5\)-4-heteroaryl-cyclohexanecarboxylic acid ester intermediate of formula VIII-b.

**4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 1**

cis/trans-4-Pyridin-2-yl-cyclohexanecarboxylic acid ethyl ester

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\end{array}
\]
The title compound was obtained as colorless oil in quantitative yield from (RS)-4-pyridin-2-yl-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (IV). MS m/e: 234 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 2

\[
\text{trans-4-Pyridin-2-yl-cyclohexanecarboxylic acid ethyl ester}
\]

The title compound was obtained as light brown oil in 86% yield from cis/trans-4-pydim-2-yl-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 234 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 3

\[
\text{cis/trans-4-(6-Methyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester}
\]

The title compound was obtained as colorless liquid in 98% yield from ((RS)-4-(6-methyl-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (IV). MS m/e: 248 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 4

\[
\text{trans-4-(6-Methyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester}
\]
The title compound was obtained as light yellow liquid in quantitative yield from \textit{cis}trans-\textit{A}-(\textit{fi}-methyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI).

MS m/e: 248 ([M+H]⁺)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 5

\textit{cis}/\textit{trans}-4-(6-Ethyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as colorless liquid in 97\% yield from ((\textit{RS})-4-(6-ethyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IV). MS m/e: 262 ([M+H]⁺)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 6

\textit{trans}-4-(6-Ethyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as colorless oil in 59\% yield from \textit{cis}/\textit{trans}-\textit{NS}-4-(6-ethyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI).
MS m/e: 262 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 7

cis/trans-4-(6-Isopropyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (2:1)

The title compound was obtained as colorless liquid in 97% yield from ((RS)-4-(6-isopropyl-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (IV). MS m/e: 276 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 8

trans-4-(6-Isopropyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as yellow oil in 61% yield from cis/trans 4-(6-isopropyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 276 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 9

cis/trans-4-(6-Methoxy-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester
The title compound was obtained as colorless liquid in 95% yield from (RS)-4-(6-methoxy-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 264 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 10

*tra*<s>-4-(6-Methoxy-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as light brown oil in quantitative yield from *cis*/*trans*-4-(6-methoxy-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 264 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 11

*tra*<s>-4-(6-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester

To a solution of *n*-4-(6-methoxy-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (0.55 g, 2.1 mmol) in *N*,*N*-dimethylformamide (21 ml) was added phosphorus oxychloride (0.96 ml, 10 mmol) at room temperature. Stirring for 2 h at 90 °C was followed by stirring for 24 h at 120 °C.
After cooling to room temperature the reaction mixture was poured onto crushed ice, stirred for 10 minutes and extracted with three 100-ml portions of ethyl acetate. The combined organic layers were washed with two 50-ml portions of water and one 50-ml portion of brine, dried over anhydrous sodium sulfate and concentrated to dryness. Purification by flash-chromatography gave the title compound (0.20 g, 36%) as light yellow oil. MS m/e: 268 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 12

cis/trans-4-(6-Amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (2:1)

The title compound was obtained as colorless liquid in 95% yield from (RS)-4-(6-amino-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 249 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 13

trans-4-(6-Amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as light yellow solid in 74% yield from cis/trans-4-(6-amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 248 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 14

trans-4-(6-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester
Batch 1: To a solution of is -4-(6-amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (0.050 g, 0.20 mmol) in 70% hydrogen fluoride in pyridine (0.47 ml, 18 mmol) was added solid sodium nitrite (0.015 g, 0.22 mmol) at 0-5 °C. The cooling bath was removed after 20 minutes and the reaction mixture was stirred for 30 minutes at room temperature. The reaction mixture was partitioned between an ice-water mixture (50 ml) and tert-butyl methyl ether (50 ml). The organic layer was collected. The aqueous layer was extracted with two 50-ml portions of tert-butyl methyl ether. The combined organic layers were washed with one 30-ml portion of 2M aqueous sodium hydroxide solution and one 30-ml portion of brine, dried over anhydrous sodium sulfate and concentrated to dryness to give the crude title compound (0.08 g).

Batch 2: To a solution of is -4-(6-amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (0.25 g, 1.0 mmol) in 70% hydrogen fluoride in pyridine (2.4 ml, 92 mmol) was added solid sodium nitrite (0.076 g, 1.1 mmol) at 0-5 °C. The cooling bath was removed after 20 minutes and the reaction mixture was stirred for 30 minutes at room temperature. The reaction mixture was partitioned between an ice-water mixture (100 ml) and tert-butyl methyl ether (100 ml). The organic layer was collected. The aqueous layer was extracted with two 100-ml portions of tert-butyl methyl ether. The combined organic layers were washed with one 30-ml portion of 2M aqueous sodium hydroxide solution, one 30-ml portion of brine, dried over anhydrous sodium sulfate and concentrated to dryness to give the crude title compound (0.145 g). The batches were combined and purified by flash-chromatography with n-heptane/ethyl acetate as eluent to give the title compound (0.16 g, 51%) as colorless oil. MS m/e: 252 ([M+H]+)
The title compound was obtained as colorless liquid in 97% yield from (RS)-4-(5-fluoro-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 252 ([M+H]+)

### 4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 16

\textbf{trans-4-(5-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester}

![Chemical structure of trans-4-(5-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester](image)

The title compound was obtained as yellow liquid in quantitative yield from \textit{cis}trans-A-(5-fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 252 ([M+H]+)

### 4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 17

\textbf{c/s/trans-4-(4-Amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (3:1)}

![Chemical structure of c/s/trans-4-(4-Amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester](image)

The title compound was obtained as light yellow oil in 91% yield from (RS)-4-(4-amino-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 249 ([M+H]+)

### 4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 18

\textbf{c/s/trans-4-(4-Amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (1:9)}
The title compound was obtained as yellow oil in 92% yield from cis/trans-4-(4-amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (3:1) according to general procedure (VI). MS m/e: 249 ([M+H]^+).

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 19

cis/trans-4-(4-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (1:6)

To a solution of cis/trans-4-(4-amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (1:9) (0.638 g, 2.57 mmol) in concentrated hydrochloric acid (11.0 ml, 128 mmol) was added in small portions sodium nitrite (4.43 g, 64.2 mmol) at 0-5 °C. The reaction mixture was allowed to warm to room temperature. Copper (I) chloride (10.7 g, 108 mmol) was added in one portion. Stirring for 2 h was followed by quenching with 32% sodium hydroxide solution (9.52 ml, 103 mmol) at 0-5 °C. The reaction mixture was partitioned between dichloromethane (50 ml) and water (20 ml). The layers were separated. The aqueous layer was extracted with two 100 ml-portions of dichloromethane. The combined organic layers were washed with one 25 ml-portion of water, dried over anhydrous sodium sulfate and concentrated in vacuo. Flash-chromatography with n-heptane/ethyl acetate as eluent gave the title compound (0.186 g, 27%) as colorless oil.

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 20

cis/trans-4-(3-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester
The title compound was obtained as colorless liquid in 97% yield from (RS)-4-(3-fluoro-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 252 ([M+H]^+).

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 21

*tra«s*-4-(3-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as colorless oil in quantitative yield from *cis/tran,s*-4-(3-fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 252 ([M+H]^+).

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 22

*cis/tran,s*-4-Pyridin-3-yl-cyclohexanecarboxylic acid ethyl ester (7:3)
The title compound was obtained as colorless oil in 89% yield from (RS)-4-pyridin-3-yl-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 234 ([M+H]^+).

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 23

trans-4-Pyridin-3-yl-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as amorphous, light brown solid in quantitative yield from cis/in ns-4-pyridin-3-yl-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 234 ([M+H]^+).

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 24

cis/trans-4-(2-Amino-pyridin-3-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as colorless oil in quantitative yield from (RS)-4-(2-amino-pyridin-3-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 249 ([M+H]^+).

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 25

trans-4-(2-Amino-pyridin-3-yl)-cyclohexanecarboxylic acid ethyl ester
The title compound was obtained as light yellow solid in 82% yield from cis/trans-4-(2-amino-pyridin-3-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 249 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 26

trans-4-(2-Chloro-pyridin-3-yl)-cyclohexanecarboxylic acid ethyl ester

To a solution of cis-4-(2-amino-pyridin-3-yl)-cyclohexanecarboxylic acid ethyl ester (0.21 g, 0.86 mmol) in concentrated hydrochloric acid (3.7 ml, 43 mmol) was added solid sodium nitrite (1.49 g, 21.5 mmol) at 0-5 °C. The cooling bath was removed and copper(I)chloride (3.58 g, 36.2 mmol) was added at room temperature. After stirring for 2 h the mixture was partitioned between water (50 ml) and ethyl acetate (50 ml). The organic layer was collected. The aqueous layer was extracted with two 50-ml portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness. Flash-chromatography with n-heptane/ethyl acetate as eluent gave the title compound (0.093 g, 44%) as yellow oil. MS m/e: 268 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 27

trans-4-(2-Fluoro-pyridin-3-yl)-cyclohexanecarboxylic acid ethyl ester
To a solution of 4-(2-amino-pyridin-3-yl)-cyclohexanecarboxylic acid ethyl ester (0.25 g, 1.0 mmol) in 70% hydrogen fluoride in pyridine (2.4 ml, 92 mmol) was added solid sodium nitrite (0.076 g, 1.1 mmol) at 0-5 °C. The cooling bath was removed after 30 minutes and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was partitioned between an ice-water mixture (50 ml) and tert-butyl methyl ether (50 ml). The organic layer was collected. The aqueous layer was extracted with one 100-ml portion of tert-butyl methyl ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness. Flash-chromatography with n-heptane/ethyl acetate as eluent gives the title compound (0.11 g, 44%) as light yellow oil. MS m/e: 252 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 28

\textit{cis/trans}-4-Pyrimidin-2-yl-cyclohexanecarboxylic acid ethyl ester (7:3)

The title compound was obtained as light brown oil in 78% yield from (RS)-4-pyrimidin-2-yl-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 235 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 29

\textit{cis/trans}-4-(4,6-Dimethyl-pyrimidin-2-yl)-cyclohexanecarboxylic acid ethyl ester (4:1)
The title compound was obtained as yellow oil in 97% yield from (RS)-4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 263 ([M+H]^+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 30

trans-4-(4,6-Dimethyl-pyrimidin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as yellow oil in 71% yield from cis/trans-4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 263 ([M+H]^+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 31

cis/trans-4-(2-Methyl-pyrimidin-4-yl)-cyclohexanecarboxylic acid ethyl ester (2:1)

The title compound was obtained as colorless liquid in 98% yield from (RS)-4-(2-methyl-pyrimidin-4-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V).
MS m/e: 249 ([M+H]⁺)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 32

trans-4-(2-Methyl-pyrimidin-4-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as brown oil in quantitative yield from cis/trans-4-(2-methyl-pyrimidin-4-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 249 ([M+H]⁺)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 33

cis/trans-4-Pyrazin-2-yl-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as colorless liquid in 72% yield from (RS)-4-(3-chloropyrazin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester and triethylamine (1 eq) as additive according to general procedure (V). MS m/e: 235 ([M+H]⁺)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 34

trans-4-Pyrazin-2-yl-cyclohexanecarboxylic acid ethyl ester
The title compound was obtained as yellow oil in quantitative yield from cis/trans-4-pyrazm-2-yl-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 235 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 35

cis/trans-4-(6-Methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as light yellow oil in quantitative yield from (RS)-4-(6-methyl-pyrazin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 249 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 36

trans-4-(6-Methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as yellow oil in 66% yield from cis/trans-4-(6-methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 249 ([M+H]+)
4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 37

cis/trans-4-(3-Methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester (2:1)

The title compound was obtained as yellow oil in 88% yield from (RS)-4-(3-methyl-pyrazin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 249 ([M+H]⁺)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 38

trans-4-(3-Methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as yellow oil in 56% yield from cis/trans-4-(3-methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 249 ([M+H]⁺)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 39

cis/trans-4-(3,6-Dimethyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester (2:1)
The title compound was obtained as yellow liquid in 90% yield from (RS)-4-(3,6-dimethyl-pyrazin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 263 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 40

trans-4-(3,6-Dimethyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as yellow oil in 89% yield from cis/trans-4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VI). MS m/e: 263 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 41

cis/trans-4-Pyridazin-3-yl-cyclohexanecarboxylic acid ethyl ester

The title compound was obtained as yellow liquid in 90% yield from (RS)-4-(6-chloro-pyridazin-3-yl)-cyclohex-3-enecarboxylic acid ethyl ester and triethylamine (1 eq) as additive according to general procedure (V). MS m/e: 235 ([M+H]+)
4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 42

cis/trans-4-(3-Amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (3:1)

The title compound was obtained as light yellow viscous oil in quantitative yield from (RS)- 4-
(3-amino-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure
(V). MS m/e: 249 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 43

cis/trans-4-(3-Amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (1:11)

The title compound was obtained as off-white solid in 46% yield from cis/trans-4-(3-amino-
pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (3:1) according to general procedure (VI).
MS m/e: 249 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 44

c/s/frans-4-(3,5-Difluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (2:1)
The title compound was obtained as light yellow oil in 99% yield from (RS)-4-(3,5-difluoro-pyridin-2-yl)-cyclohex-3-enecarboxylic acid ethyl ester according to general procedure (V). MS m/e: 270 ([M+H]⁺)

4-Heteroaryl-cyclohexanecarboxylic acid ester intermediate 45

trans-4-(3,5-Difluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (1:9)

The title compound was obtained as light yellow oil in 25% yield from cis/trans-4-(3,5-difluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (2:1) according to general procedure (VI). MS m/e: 270 ([M+H]⁺)

4-Heteroaryl-cyclohexanecarboxylic acid intermediates of formula (IX)

General procedure (VII): Saponification

A solution of a 4-heteroaryl-cyclohexanecarboxylic acid ester of formula VII in 1,4-dioxane (0.1 M) and 2M aqueous sodium hydroxide solution (10 eq) is stirred at room temperature for 20 h. The reaction mixture is partitioned between an organic solvent such as ethyl acetate or tert-butyl methyl ether and water. The organic layer is extracted with one or two portions of 0.5 M aqueous sodium hydroxide solution. The aqueous layer is acidified by addition of 2M aqueous hydrogen chloride solution and extracted with two or three portions of organic solvent. The combined organic extracts are dried over anhydrous sodium sulfate and concentrated to dryness to give a 4-heteroaryl-cyclohexanecarboxylic acid of formula IX, which can usually be used in the next step without further purification.
4-Heteroaryl-cyclohexanecarboxylic acid 1

trans-4-(6-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid

The title compound was obtained as white solid in 98% yield from its 4-(6-chloro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VII). MS m/e: 238 ([M-\text{H}])

4-Heteroaryl-cyclohexanecarboxylic acid 2

trans-4-(6-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid

The title compound was obtained as white solid in quantitative yield from its 4-(6-fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VII). MS m/e: 222 ([M-\text{H}])

4-Heteroaryl-cyclohexanecarboxylic acid 3

cis/trans-4-(4-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid
The title compound was obtained as white solid in 78% yield from cis/trans-4-(4-chloro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (1:6) according to general procedure (VII). MS m/e: 238 ([M-ΗΓ])

**4-Heteroaryl-cyclohexanecarboxylic acid 4**

*trans*-4-(2-Chloro-pyridin-3-yl)-cyclohexanecarboxylic acid

The title compound was obtained as white solid in 97% yield from *trans*-4-(2-chloro-pyridin-3-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VII). MS m/e: 238 ([M-ΗΓ])

**4-Heteroaryl-cyclohexanecarboxylic acid 5**

*trans*-4-(2-Fluoro-pyridin-3-yl)-cyclohexanecarboxylic acid

The title compound was obtained as off-white solid in 97% yield from *trans*-4-(2-fluoro-pyridin-3-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (VII). MS m/e: 222 ([M-ΗΓ])

**4-Heteroaryl-cyclohexanecarboxylic acid 6**

*cis/trans*-4-Pyrimidin-2-yl-cyclohexanecarboxylic acid (2:1)
The title compound was obtained as off-white solid in 70% yield from cis/trans-4-pyrimidm-2-yl-cyclohexanecarboxylic acid ethyl ester according to general procedure (VII). MS m/e: 205 ([M-H⁺])

4-Heteroaryl-cyclohexanecarboxylic acid 7

cis/trans-4-Pyridazin-3-yl-cyclohexanecarboxylic acid (3:2)

The title compound was obtained as brown solid in quantitative yield from cis/trans-4-pyridazin-3-yl-cyclohexanecarboxylic acid ethyl ester according to general procedure (VII). MS m/e: 205 ([M-H⁺])

4-Heteroaryl-cyclohexanecarboxylic acid 8

in nS-4-(3-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid

To a solution of cis/in nS-4-(3-amino-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (1:11) (0.570 g, 2.30 mmol) in concentrated hydrochloric acid (37%; 20 ml) was added sodium nitrite (0.292 g, 4.23 mmol) in small portions at 0-5 °C. Stirring for 20 minutes was followed by addition of copper (I) chloride (0.493 g, 4.83 mmol) in one portion. After 10 minutes the reaction mixture was heated to 65 °C (oil bath temperature). The temperature was maintained at 65 °C for 20 h. The reaction mixture was cooled to 0-5 °C and adjusted to pH 4 by addition of aqueous sodium hydroxide solution (32%; 20 ml). The green aqueous layer was extracted with three 75 ml-portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography over SiO₂
with n-heptane/ethyl acetate as eluent to give the title compound (0.424 g, 77%) as off-white solid. MS m/e: 240 ([M+H]+)

4-Heteroaryl-cyclohexanecarboxylic acid 9

\[
\text{trans-4-(3,5-Difluoro-pyridin-2-yl)-cyclohexanecarboxylic acid}
\]

The title compound was obtained as off-white solid in quantitative yield from \textit{cis/trans-4-(3,5-difluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester (1:9) according to general procedure (VII). MS m/e: 240 ([M-H]−)}

**Hydrazide intermediates of formula (II)**

**General procedure (VIII):** Hydrazide formation from acid

To a solution of a 4-heteroaryl-cyclohexanecarboxylic acid intermediate of formula (IX) (1 eq) and triethylamine (1.05 eq) in tetrahydrofuran (0.2 M) is added ethyl chloroformate (1.05 eq) at 0 °C. The reaction mixture is stirred at 0 °C for 1 h. The ammonium salts are removed by filtration. The filtrate is added to a cold solution of hydrazine hydrate (2 eq) in methanol (0.2 M). The reaction mixture is stirred at room temperature for 2-16 h. The solvent is evaporated under reduced pressure, and the residue is partitioned between an organic solvent such as ethyl acetate or dichloromethane and water. The organic layer is separated. The aqueous layer is extracted with two or three portions of organic solvent. The combined organic layers are dried over anhydrous sodium sulfate and concentrated in vacuo to give a hydrazide intermediate of formula (II), which is usually used in the next step without further purification.

**General procedure (IX):** Hydrazide formation from ester

A mixture of a 4-heteroaryl-cyclohexanecarboxylic acid ester intermediate of formula (VIII) (1 eq) and hydrazine hydrate (2-6 eq) in n-butanol (0.2-1 M) is heated at reflux for 16-72 h. After cooling to room temperature the reaction mixture is partitioned between an organic solvent such as ethyl acetate or dichloromethane and water. The layers are separated and the aqueous layer is extracted with two portions of organic solvent. The combined organic layers are dried over anhydrous sodium sulfate and concentrated in vacuo to give a hydrazide intermediate of formula (II), which is usually used in the next step without further purification.
Hydrazide 1

trans-4-Pyridin-2-yl-cyclohexanecarboxylic acid hydrazide

The title compound was obtained as white solid in 84% yield from in trans-4-pyridin-2-yl-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 220 ([M+H]+)

Hydrazide 2

trans-4-(6-Methyl-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

The title compound was obtained as white solid in 44% yield from in 4-(6-methyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 234 ([M+H]+)

Hydrazide 3

trans-4-(6-Ethyl-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide
The title compound was obtained as white solid in 66% yield from \( n_s 4\)-(6-ethyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 248 ([M+H]+)

**Hydrazide 4**

\( \text{trans}-4\)-(6-isopropyl-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

![Chemical structure](image1)

The title compound was obtained as yellow solid in 98% yield from \( n_s 4\)-(6-isopropyl-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 262 ([M+H]+)

**Hydrazide 5**

\( \text{trans}-4\)-(6-Methoxy-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

![Chemical structure](image2)

The title compound was obtained as white solid in 81% yield from \( n_s 4\)-(6-methoxy-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 250 ([M+H]+)

**Hydrazide 6**

\( \text{trans}-4\)-(6-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide
The title compound was obtained as white solid in 84% yield from 4-(6-chloropyridin-2-yl)-cyclohexanecarboxylic acid according to general procedure (VIII). MS m/e: 254 ([M+H]⁺)

**Hydrazide 7**

trans-4-(6-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

The title compound was obtained as off-white solid in 92% yield from 4-(6-fluoropyridin-2-yl)-cyclohexanecarboxylic acid according to general procedure (VIII). MS m/e: 238 ([M+H]⁺)

**Hydrazide 8**

trans-4-(5-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

The title compound was obtained as white solid in 69% yield from 4-(5-fluoropyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 238 ([M+H]⁺)
Hydrazide 9

cis/trans-4-(4-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

\[
\text{N} \quad \text{O} \\
\text{N} \quad \text{NH} \\
2
\]

The title compound was obtained as white solid in 74% yield from cis in 4-(4-chloro-pyridin-2-yl)-cyclohexanecarboxylic acid according to general procedure (VIII). MS m/e: 254 ([M+H]+)

Hydrazide 10

trans-4-(3-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

\[
\text{N} \quad \text{O} \\
\text{NH} \quad \text{NH}_2
\]

The title compound was obtained as white solid in quantitative yield from in 4-(3-fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 238 ([M+H]+)

Hydrazide 11

cis/trans-4-(3-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide (7.8:1)

\[
\text{N} \quad \text{O} \\
\text{NIL}_2
\]
The title compound was obtained as white solid in 91% yield from cis-4-(3-fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 238 ([M+H]+)

Hydrazide 12

\textit{trans-4-Pyridin-3-yl-cyclohexanecarboxylic acid hydrazide}

The title compound was obtained as light yellow solid in 53% yield from cis-4-pyridin-3-yl-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 220 ([M+H]+)

Hydrazide 13

\textit{trans-4-(2-Chloro-pyridin-3-yl)-cyclohexanecarboxylic acid hydrazide}

The title compound was obtained as white solid in 97% yield from cis-4-(2-chloro-pyridin-3-yl)-cyclohexanecarboxylic acid according to general procedure (VIII). MS m/e: 254 ([M+H]+)

Hydrazide 14

\textit{trans-4-(2-Fluoro-pyridin-3-yl)-cyclohexanecarboxylic acid hydrazide}
The title compound was obtained as white solid in 82% yield from n-is-(2-fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid according to general procedure (VIII). MS m/e: 238 ([M+H]⁺)

**Hydrazide 15**

\[
\text{cis}/\text{trans}-4-\text{Pyrimidin-2-yl-cyclohexanecarboxylic acid hydrazide}
\]

The title compound was obtained as white solid in 81% yield from \textit{cis}/\textit{trans}-4-pyrimidin-2-yl-cyclohexanecarboxylic acid according to general procedure (VIII). MS m/e: 221 ([M+H]⁺)

**Hydrazide 16**

\[
\text{trans}-4-(4,6-\text{Dimethyl-pyrimidin-2-yl)-cyclohexanecarboxylic acid hydrazide}
\]

The title compound was obtained as white solid in 87% yield from \textit{cis}/\textit{trans}-4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 249 ([M+H]⁺)
*trans*-4-(2-Methyl-pyrimidin-4-yl)-cyclohexanecarboxylic acid hydrazide

![Chemical structure](image)

The title compound was obtained as off-white solid in 58% yield from *trans*-4-(2-methyl-pyrimidin-4-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 235 ([M+H]⁺)

**Hydrazide 18**

*trans*-4-(Pyrazin-2-yl)-cyclohexanecarboxylic acid hydrazide

![Chemical structure](image)

The title compound was obtained as yellow solid in quantitative yield from *trans*-4-(pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX).

**Hydrazide 19**

*trans*-4-(6-Methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid hydrazide

![Chemical structure](image)
The title compound was obtained as white solid in 82% yield from $n$-4-(6-methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 235 ([M+H]$^+$)

**Hydrazide 20**

$\textit{trans}$-$4$-$($3$-$Methyl$-$pyrazin$-$2$-$yl$)$-$cyclohexanecarboxylic$ acid$ hydrazide

The title compound was obtained as white solid in 73% yield from $n$-4-(3-methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 235 ([M+H]$^+$)

**Hydrazide 21**

$\textit{trans}$-$4$-$($3$,$6$$-$Dimethyl$-$pyrazin$-$2$-$yl$)$-$cyclohexanecarboxylic$ acid$ hydrazide

The title compound was obtained as white solid in 90% yield from $n$-4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexanecarboxylic acid ethyl ester according to general procedure (IX). MS m/e: 249 ([M+H]$^+$)

**Hydrazide 22**

$\textit{cis}$/\textit{trans}$-$4$-$Pyridazin$-$3$-$yl$-$cyclohexanecarboxylic$ acid$ hydrazide
The title compound was obtained as white solid in quantitative yield from cis/trans-4-pyridazin-3-yl-cyclohexanecarboxylic acid according to general procedure (VIII). MS m/e: 221 ([M+H]⁺)

**Hydrazide 23**

trans-4-(3-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

The title compound was obtained as white solid in 97% yield from 4-(3-chloro-pyridin-2-yl)-cyclohexanecarboxylic acid according to general procedure (VIII). MS m/e: 254 ([M+H]⁺)

**Hydrazide 24**

\( \sigma_{\text{trans}} \)-4-(3,5-Difluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

The title compound was obtained as white solid in 67% yield from 4-(3,5-difluoro-pyridin-2-yl)-cyclohexanecarboxylic acid according to general procedure (VIII). MS m/e: 256 ([M+H]⁺)

**Thiolactam intermediates of formula III**
a) 4-Chloro-2-chloromethyl-1-nitro-benzene

To a solution of 5-chloro-2-nitrobenzyl alcohol (80 g, 0.42 mol) and triethylamine (64 ml, 0.46 mol) in dichloromethane (840 ml) was added drop wise thionyl chloride (34 ml, 0.46 mol) during a period of 30 minutes while the internal temperature was kept below 32 °C by cooling with a water bath. The reaction mixture was stirred for 3 h. The solvent was evaporated and the residue was triturated in warm iert-butyl methyl ether (970 ml). The ammonium salts were removed by filtration and the filtrate was concentrated in vacuo to give the title compound (85 g, 99%) as brown oil which was used in the next step without purification. MS m/e: 205 (M+).

b) (5-Chloro-2-nitro-benzylamino)-acetic acid ethyl ester

A mixture of 4-chloro-2-chloromethyl-1-nitro-benzene (85 g, 0.41 mol), glycine ethyl ester hydrochloride (70 g, 0.50 mol) and triethylamine (121.4 ml, 0.8665 mol) in ethanol (1000 ml) was heated at reflux for 8 h. The solvent was evaporated and the residue was triturated in warm iert-butyl methyl ether. The ammonium salts were removed by filtration and the filtrate was concentrated in vacuo to give the title compound (111 g, 99%) as an amorphous brown solid which was used in the next step without purification. MS m/e: 273 (M+H+).

c) tert-Butoxycarbonyl-(5-chloro-2-nitro-benzyl)-aminol-acetic acid ethyl ester

A solution of (5-chloro-2-nitro-benzylamino)-acetic acid ethyl ester (110 g, 0.403 mol), αi-tert-butyl dicarbonate (180 g, 0.807 mol) and 4-N,N-dimethylaminopyridine (2.51 g, 0.0202 mol) in dichloromethane (1200 ml) was stirred for 2 h at 0 °C and further 16 h at room temperature. The solvent was evaporated and the crude product was purified by flash chromatography with a cyclohexane/ethyl acetate mixture as eluent to give the title compound (76.4 g, 51%) as light yellow viscous oil. MS m/e: 373 (M+H+).

d) [(2-Amino-5-chloro-benzyl)-fer?-butoxycarbonyl-aminol -acetic acid ethyl ester

To a solution of [ieri-butoxycarbonyl-(5-chloro-2-nitro-benzyl)-amino] -acetic acid ethyl ester (69.0 g, 0.186 mol) in ethyl acetate (1200 ml) was added zinc bromide (8.5 g, 0.037 mol). The reaction mixture was purged with argon after 15 minutes. After addition of the palladium catalyst (10% on activated charcoal, 7.9 g, 0.0074 mol) the mixture was hydrogenated at ambient pressure during a period of ca. 48 h until ca. 13 l of hydrogen gas had been consumed. The catalyst was removed by filtration and the filtrate was washed with two portions of saturated aqueous sodium bicarbonate solution and brine, each. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give the title compound (60.6 g, 95.5%) as yellow waxy solid. MS m/e: 343 (M+H+).
e) 7-Chloro-2-oxo-1,2,3,5-tetrahydro-benzori,41diazepine-4-carboxylic acid tert-butyl ester

To a solution of [(2-amino-5-chloro-benzyl)-iert-butoxycarbonyl-amino] -acetic acid ethyl ester (60 g, 0.18 mol) in tetrahydrofuran (600 ml) was added potassium tert-butoxide (22 g, 0.19 mol) in small portions at 5 °C under cooling on an ice-water batch. After completed addition the cooling bath was removed and reaction mixture was stirred for 3 h at room temperature followed by addition of water (400 ml), saturated aqueous ammonium chloride solution (280 ml) and ethyl acetate (800 ml). After 10 minutes the precipitate was collected by filtration. The layers were separated from the filtrate, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was combined with the precipitate, which had previously been collected by filtration, and crystallized from hot ethyl acetate to give the title compound (46 g, 88%) as white solid. MS m/e: 295 (M-H+).

f) 7-Chloro-2-thioxo-l,23,5-tetrahydro-benzoreiri,41diazepine-4-carboxylic acid tert-butyl ester

A mixture of 7-chloro-2-oxo- 1,2,3,5-tetrahydro-benzo[I,4]diazepine-4-carboxylic acid iert-butyl ester (41.1 g, 0.139 mol) and 2,4-bis-(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (31.5 g, 0.0763 mol) in tetrahydrofuran (1100 ml) was heated at reflux for 3 h. The solvent was evaporated and the residue was triturated in iert-butyl methyl ether. The precipitate was removed by filtration and the filtrate was concentrated to dryness. The residue was crystallized from hot ethanol to give the title compound (37.5 g, 86.4%) as light yellow solid. MS m/e: 311 (M-H+).

20) 7-Fluoro-2-thioxo-l,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester

The title compound was obtained as light yellow solid in comparable yields according to the procedures described above for the synthesis of 7-chloro-2-thioxo- 1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester using 5-fluoro-2-nitrobenzyl alcohol instead of 5-chloro-2-nitrobenzyl alcohol in step a). MS m/e: 297 (M-H+).

**General procedure (X): Condensation of hydrazide and thiolactam to triazole**

A mixture of a hydrazide of formula II (1-1.5 eq) and a thiolactam of formula III (1 eq) in n-butanol (0.1-0.2 M) is heated at reflux for 16-72 h. After cooling to room temperature the solvent is evaporated and the residue is purified by flash-chromatography to give a compound of formula I. When a thiolactam of formula III-1 (compounds of formula III in which R1 is tert-butoxycarbonyl) is used the N-iert-butoxycarbonyl group of the resulting triazole product of formula 1-1 can be partially or completely cleaved thermally, and a secondary amine of formula 1-2 is obtained in addition or as the sole product.

**General procedure (XI-a): Cleavage of N-tert-butoxycarbonyl (N-BOC) group**
A solution of an N-BOC derivative of formula 1-1 (1 eq) in 1.25 M methanolic or 1.5 M ethanolic hydrogen chloride solution (10 - 20 eq HCl) is heated at 50 °C for 15-60 minutes. After cooling to room temperature the reaction mixture is concentrated in vacuo to give a secondary amine of formula 1-2 as hydrochloride salt. Optionally the free base can be obtained by partitioning the hydrochloride salt between 1 M aqueous sodium hydroxide solution and an organic solvent, e.g. ethyl acetate or dichloromethane. The layers are separated and the aqueous layer is extracted with two portions of the organic solvent. The combined organic layers are dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give the free base of a compound of formula 1-2.

**General procedure (XI-b): Cleavage of N-tert-butoxycarbonyl (N-BOC) group**

A solution of an N-BOC derivative of general formula 1-1 (1 eq) and trifluoroacetic acid (10-20 eq) in dichloromethane is stirred at room temperature for 6-24 h. The reaction mixture is partitioned between 1 M aqueous sodium hydroxide solution and an organic solvent such as ethyl acetate or dichloromethane. The layers are separated and the aqueous layer is extracted with two portions of the organic solvent. The combined organic layers are dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give the free base of a compound of formula 1-2.

**General procedure (XII): Reductive N-alkylation**

A mixture of a compound of formula 1-2 as free base or as hydrochloride salt (1 eq, 0.1-0.2 M), triethylamine (1 eq when the hydrochloride salt of a compound of formula 1-2 is used) and an aldehyde or ketone (8 eq) in methanol is heated at reflux for 2-6 h. After cooling to 0 °C sodium cyanoborohydride (2-3 eq) is added. The reaction mixture is stirred for 3-16 h at room temperature and quenched with 1 M aqueous sodium hydroxide solution. The aqueous layer is extracted with ethyl acetate. The combined organic layers are dried over anhydrous sodium sulfate and concentrated in vacuo. Flash chromatography gives an N-alkyl compound of formula 1.

**General procedure (XIII): Reductive N-methylation**

A mixture of a compound of formula 1-2 as free base (1 eq, 0.1-0.2 M), sodium acetate (1.1 eq), acetic acid (1.1 eq) and an aqueous formaldehyde solution (36%, 1.4 eq) in dichloromethane is stirred for 0.5-2 h. After cooling to 0 °C sodium triacetoxyborohydride (1.6 eq) is added. The reaction mixture is stirred for 2-16 h at room temperature and quenched with 1 M aqueous sodium hydroxide solution. The aqueous layer is extracted with ethyl acetate. The combined organic layers are dried over anhydrous sodium sulfate and concentrated in vacuo. Flash chromatography gives an N-methyl compound of formula 1-3.

**Example 1**
trans-8-Chloro-1-(4-pyridin-2-yl-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white solid in 72% yield according to general procedure (X).

Hydrazide: in nS-4-Pyridin-2-yl-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 480 ([M+H]+)

Example 2

trans-8-Chloro-1-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene dihydrochloride

The title compound was obtained as white solid in quantitative yield from in nS-8-chloro-1-(4-pyridin-2-yl-cyclohexyl)-4H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester according to general procedure (XI-a). MS m/e: 380 ([M+H]+)

Example 3

trans-8-Chloro-5-methyl-1-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene

The title compound was obtained as white solid in 46% yield from in nS-8-chloro-1-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene dihydrochloride and paraformaldehyde according to general procedure (XII). MS m/e: 394 ([M+H]+)

Example 4

trans-8-Chloro-1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as off-white solid in 77% yield according to general procedure (X).

Hydrazide: in nS-4-(6-Methyl-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 494 ([M+H]+)

Example 5

trans-8-Chloro-1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene
The title compound was obtained as white solid in quantitative yield from 1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-4-H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure (X1-a). MS m/e: 394 ([M+H]^+).

Example 6

trans-8-Chloro-1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

The title compound was obtained as white solid in 59% yield from 1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 408 ([M+H]^+).

Example 7

trans-8-Chloro-1-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[>]azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white solid in 48% yield according to general procedure (X). Hydrazide: in 1-[4-(6-Ethyl-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 508 ([M+H]^+)

Example 8

trans-8-Chloro-1-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

The title compound was obtained as off-white solid in 83% yield from 1-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure (X1-a). MS m/e: 408 ([M+H]^+).

Example 9

trans-8-Chloro-1-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

The title compound was obtained as white solid in 67% yield from 1-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 422 ([M+H]^+).

Example 10
The title compound was obtained as light yellow solid in 55% yield according to general procedure (X).

Hydrazide: in \( n\)-4-(6-Isopropyl-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 522 ([M+H]+)

Example 11

The title compound was obtained as light yellow solid in quantitative yield from \( n\)-8-chloro-l-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e] azulene-5-carboxylic acid tert-butyl ester according to general procedure (XI-a). MS m/e: 422 ([M+H]+)

Example 12

The title compound was obtained as white solid in 50% yield from \( n\)-8-chloro-l-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e] azulene hydrochloride and paraformaldehyde according to general procedure (XII). MS m/e: 436 ([M+H]+)

Example 13

The title compound was obtained as white solid in 40% yield according to general procedure (X). Hydrazide: in \( n\)-4-(6-Methoxy-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 510 ([M+H]+)

Example 14

The title compound was obtained as light yellow solid in 40% yield according to general procedure (X). Hydrazide: in \( n\)-4-(6-Methoxy-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 510 ([M+H]+)
The title compound was obtained as white solid in 53% yield from \( \text{NS}-8\text{-chloro-L-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-4\text{\,H,6H}-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester} \) according to general procedure (XI-a). MS m/e: 410 ([M+H]⁺)

**Example 15**

*trans-8-Chloro-L-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4\text{\,H,2,3,5,10b-tetraaza-benzo|>]azulene*  
The title compound was obtained as white solid in 48% yield from \( \text{NS}-8\text{-chloro-L-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4\text{\,H}-2,3,5,10b-tetraaza-benzo[e]azulene} \) and paraformaldehyde according to general procedure (XII). MS m/e: 424 ([M+H]⁺)

**Example 16**

*trans-8-Chloro-L-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-4\text{\,H,6H}-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester*  
The title compound was obtained as white solid in 66% yield according to general procedure (X). Hydrazide: \( \text{NS}\text{-4-(6-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide} \)  
Thiolactam: \( 7\text{-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester} \)  
MS m/e: 514.5 ([M+H]⁺)

**Example 17**

*trans-8-Chloro-L-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4\text{\,H}-2,3,5,10b-tetraaza-benzo|>]azulene*  
The title compound was obtained as off-white solid in quantitative yield from \( \text{inms-S-chloro-L-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-4\text{\,H,6H}-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester} \) according to general procedure (XI-b). MS m/e: 414 ([M+H]⁺)

**Example 18**

*trans-8-Chloro-L-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4\text{\,H}-2,3,5,10b-tetraaza-benzo|>]azulene*  
The title compound was obtained as white solid in 41% yield from \( \text{NS}-8\text{-chloro-L-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4\text{\,H}-2,3,5,10b-tetraaza-benzo[e]azulene} \) and paraformaldehyde according to general procedure (XII). MS m/e: 428 ([M+H]⁺)

**Example 19**
trans-8-Chloro-1-[4-(6-fluoro-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as off-white solid in 69% yield according to general procedure (X).

Hydrazide: in nS-4-(6-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide
Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid tert-butyl ester.
MS m/e: 498 ([M+H]+)

Example 20

trans-8-Chloro-1-[4-(6-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H,2,3,5,10b-tetraaza-benzo]azulene

The title compound was obtained as off-white solid in quantitative yield from inns-S-chloro-1-[4-(6-fluoro-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure (XI-b). MS m/e: 398 ([M+H]+)

Example 21

trans-8-Chloro-1-[4-(6-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H,2,3,5,10b-tetraaza-benzo]azulene

The title compound was obtained as white solid in 63% yield from inns-8-chloro-1-[4-(6-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H,2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 412 ([M+H]+)

Example 22

trans-8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo]azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as light yellow solid in 57% yield according to general procedure (X).

Hydrazide: in nS-4-(5-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide
Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid tert-butyl ester.
MS m/e: 498 ([M+H]+)

Example 23

trans-8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H,2,3,5,10b-tetraaza-benzo]azulene dihydrochloride
The title compound was obtained as off-white solid in quantitative yield from \( \text{iraw}^\circ \text{S-chloro-l-}[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester \) according to general procedure (XI-a). MS m/e: 398 ([M+H]+)

**Example 24**

\[ \text{trans-8-Chloro-l-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H,6H-2,3,5,10b-tetraaza-benzo} \text{|\rangle azulene} \]

The title compound was obtained as white solid in 91% yield from \( \text{ns-8-chloro-l-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene dihydrochloride} \) and paraformaldehyde according to general procedure (XII). MS m/e: 412 ([M+H]+)

**Example 25**

\[ \text{trans-8-Chloro-l-[4-(4-chloro-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo} \text{|\rangle azulene-5-carboxylic acid tert-butyl ester} \]

The title compound was obtained as white solid in 5% yield according to general procedure (X). Hydrazide: \( \text{cis/sia ns-4-(4-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide} \)
Thiolactam: \( \text{7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester} \)
MS m/e: 514 ([M+H]+)

**Example 26**

\[ \text{trans-8-Chloro-l-[4-(4-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo} \text{|\rangle azulene} \]

The title compound was obtained as off-white solid in 87% yield from \( \text{ns-8-chloro-l-[4-(4-chloro-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester} \) according to general procedure (XI-b). MS m/e: 414 ([M+H]+)

**Example 27**

\[ \text{trans-8-Chloro-l-[4-(4-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo} \text{|\rangle azulene} \]

The title compound was obtained as white solid in 35% yield from \( \text{ns-8-chloro-l-[4-(4-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \) and paraformaldehyde according to general procedure (XII). MS m/e: 428 ([M+H]+)

**Example 28**
The title compound was obtained as light brown solid in 64% yield according to general procedure (X).

5 Hydrazide: in \(nS\)-4-(3-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester.

MS m/e: 498 ([M+H]⁺)

Example 29

10 \(trans\)-8-Chloro-4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4\(H\)-2,3,5,10b-tetraaza-benzo[\(\tau\)]azulene

The title compound was obtained as off-white solid in 99% yield from in \(nS\)-8-chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4 \(H\)-2,3,5,10b-tetraaza-benzo[\(e\)]azulene-5-carboxylic acid tert-butyl ester according to general procedure (XI-b). MS m/e: 398 ([M+H]⁺)

Example 30

\(trans\)-8-Chloro-4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 \(H\)-2,3,5,10b-tetraaza-benzo[\(\tau\)]azulene

The title compound was obtained as white solid in 46% yield from in \(nS\)-8-chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \(H\)-2,3,5,10b-tetraaza-benzo[\(e\)]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 412 ([M+H]⁺)

Example 31

\(trans\)-8-Chloro-5-ethyl-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \(H\)-2,3,5,10b-tetraaza-benzo[\(\tau\)]azulene

The title compound was obtained as off-white solid in 18% yield from in \(nS\)-8-chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \(H\)-2,3,5,10b-tetraaza-benzo[\(e\)]azulene and acetaldehyde according to general procedure (XII). MS m/e: 426 ([M+H]⁺)

Example 32

\(trans\)-8-Chloro-5-isopropyl-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \(H\)-2,3,5,10b-tetraaza-benzo[\(\tau\)]azulene

After stirring a solution of in \(nS\)-8-chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-\(4H\)-2,3,5,10b-tetraaza-benzo[\(e\)]azulene (50.0 mg, 0.126 mmol), acetone (0.019 ml, 0.251 mmol)
and acetic acid (0.014 ml, 0.25 mmol) in 1,2-dichloroethane (1.3 ml) at room temperature for 5 h, sodium triacetoxyborohydride (58.6 mg, 0.276 mmol) was added. Stirring for further 20 h was followed by quenching with methanol (1 ml) and N-ethylidiisopropylamine (0.044 ml, 0.25 mmol). The reaction mixture was stirred for 30 minutes and concentrated in vacuo. Preparative RP-HPLC with water (0.05% formic acid) / methanol as eluent gave the title compound (40 mg, 72%) as white solid. MS m/e: 440 ([M+H]+)

**Example 33**

\textit{trans-8-Chloro-5-cyclobutyl-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H -2,3,5,10b-tetraaza-benzo[\textregistered]azulene}

The title compound was obtained as light yellow solid in 36% yield from in \( \textit{NS}-8\)-chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H -2,3,5,10b\)-tetraaza-benzo[\textregistered]azulene and cyclobutanone according to general procedure (XII). MS m/e: 452 ([M+H]+)

**Example 34**

\textit{trans-8-Chloro-5-(2,2-difluoro-ethyl)-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H -2,3,5,10b-tetraaza-benzo[\textregistered]azulene}

A mixture of \( \textit{NS}-8\)-chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H -2,3,5,10b\)-tetraaza-benzo[\textregistered]azulene (50.0 mg, 0.126 mmol), cesium carbonate (81.9 mg, 0.251 mmol) and 2,2-difluoroethyl trifluoromethanesulfonate (53.8 mg, 0.251 mmol) in acetonitrile (0.6 ml) was stirred at room temperature for 20 h. The reaction mixture was partitioned between a water-brine mixture (1:1) (2 ml) and ethyl acetate (5 ml). The layers were separated. The aqueous layer was extracted with two 5-ml portions of ethyl acetate. The combined organic layers were concentrated in vacuo. Preparative RP-HPLC with water (0.05% formic acid) / methanol as eluent gave the title compound (24 mg, 37%) as off-white solid. MS m/e: 462 ([M+H]+)

**Example 35**

\textit{trans-8-Chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5-(2-methoxy-ethyl)-5,6-dihydro-4H -2,3,5,10b-tetraaza-benzo[\textregistered]azulene}

A mixture of \( \textit{NS}-8\)-chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H -2,3,5,10b\)-tetraaza-benzo[\textregistered]azulene (50.0 mg, 0.126 mmol), cesium carbonate (81.9 mg, 0.251 mmol) and 2-bromoethyl methyl ether (0.024 ml, 0.25 mmol) in acetonitrile (0.6 ml) was heated at 70 °C for 20 h. The reaction mixture was partitioned between a water-brine mixture (1:1) (2 ml) and ethyl acetate (5 ml). The layers were separated. The aqueous layer was extracted with two 5-ml portions of ethyl acetate. The combined organic layers were concentrated in vacuo. Preparative RP-HPLC with water (0.05% formic acid) / methanol as eluent gave the title compound (13 mg, 23%) as light yellow solid. MS m/e: 456 ([M+H]+)
Example 36

\textit{trans-(2-{8-Chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4 H.6H -2,3,5,10b-tetraaza-benzo[e]azulen-5-yl}-ethyl)-methyl-amine}

A mixture of in \textit{N\textsubscript{S}-8-chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene} (50.0 mg, 0.126 mmol), cesium carbonate (246 mg, 0.754 mmol) and 2-methylaminoethyl chloride hydrochloride (65.4 mg, 0.503 mmol) in acetonitrile (1.3 ml) was heated at 70 °C for 20 h. After addition of further portions of cesium carbonate (246 mg, 0.754 mmol) and 2-methylaminoethyl chloride hydrochloride (65.4 mg, 0.503 mmol) the mixture was heated at 70 °C for another 20 h. The reaction mixture was partitioned between 1 M aqueous sodium hydroxide solution (2 ml) and ethyl acetate (5 ml). The layers were separated. The aqueous layer was extracted with two 5-ml portions of ethyl acetate. The combined organic layers were concentrated in vacuo. Preparative RP-HPLC with water (0.05% formic acid) / methanol as eluent gave the title compound as formate salt. The salt was partitioned between ethyl acetate (15 ml) and 1 M aqueous sodium hydroxide solution (10 ml). The layers were separated. The aqueous layer was extracted with two 15 ml-portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give the title compound (14 mg, 25%) as off-white solid. MS m/e: 455 ([M+H]\textsuperscript{+})

Example 37

\textit{trans-l-[8-Chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4 H.6H -2,3,5,10b-tetraaza-benzo[\textgreater]azulen-5-yl]-ethanone}

To a solution of in \textit{N\textsubscript{S}-8-chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene} (50.0 mg, 0.126 mmol) and triethylamine (0.035 ml, 0.25 mmol) in dichloromethane (0.6 ml) was added acetyl chloride (0.18 ml, 0.251 mmol) at room temperature. Stirring for 20 h was followed by partitioning between a water-brine mixture (1:1) (2 ml) and ethyl acetate (5 ml). The layers were separated. The aqueous layer was extracted with two 5 ml-portions of ethyl acetate. The combined organic layers were concentrated in vacuo. Preparative RP-HPLC with water (0.05% formic acid) / methanol as eluent gave the title compound (7 mg, 12%) as off-white solid. MS m/e: 440 ([M+H]\textsuperscript{+})

Example 38

\textit{trans-l-[8-Chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4 H.6H -2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-2-hydroxy-ethanone}

A solution of glycolic acid (11.5 mg, 0.151 mmol) and HATU (57.3 mg, 0.151 mmol) in N,N-dimethylformamide (1.0 ml) was stirred at room temperature for 5 minutes. in \textit{N\textsubscript{S}-8-Chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene} (50.0
mg, 0.126 mmol) and N-ethylisopropylamine (0.053 ml, 0.30 mmol) were added consecutively. The reaction mixture was stirred for 1 h. Preparative RP-HPLC with water (0.05% formic acid) / methanol as eluent gave the title compound (41 mg, 71%) as white solid. MS m/e: 456 ([M+H]^+)

Example 39

trans-l-[8-Chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-yl]-2-dimethylamino-ethanone formate

A solution of N,N-dimethylglycine (11.5 mg, 0.151 mmol) and HATU (57.3 mg, 0.151 mmol) in N,N-dimethylformamide (1.0 ml) was stirred for 5 minutes at room temperature. iraw^-S-Chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene (50.0 mg, 0.126 mmol) and N-ethylisopropylamine (0.053 ml, 0.30 mmol) were added consecutively. The reaction mixture was stirred for 1 h. Preparative RP-HPLC with water (0.05% formic acid) / methanol as eluent gave the title compound (51 mg, 77%) as white solid. MS m/e: 483 ([M+H]^+)

Example 40

trans-8-Chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5-methanesulfonyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

To a solution of ia N8-8-chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene (50.0 mg, 0.126 mmol) and triethylamine (0.035 ml, 0.25 mmol) in dichloromethane (0.6 ml) was added methanesulfonyl chloride (0.20 ml, 0.25 mmol) at room temperature. Stirring for 20 h was followed by partitioning between a water-brine mixture (1:1) (2 ml) and ethyl acetate (5 ml). The layers were separated. The aqueous layer was extracted with two 5 ml-portions of ethyl acetate. The combined organic layers were concentrated in vacuo. Preparative RP-HPLC with water (0.05% formic acid) / methanol as eluent gave the title compound (46 mg, 77%) as white solid. MS m/e: 476 ([M+H]^+)

Example 41

trans-8-Chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-sulfonic acid dimethylamide

To a solution of ia N8-8-chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene (50.0 mg, 0.126 mmol) and triethylamine (0.035 ml, 0.251 mmol) in dichloromethane (0.6 ml) was added dimethyl sulfamoyl chloride (0.27 ml, 0.251 mmol) at room temperature. Stirring for 20 h was followed by quenching with methanol (0.5 ml). The mixture was concentrated in vacuo. Preparative RP-HPLC with water (0.05% formic acid) / methanol as eluent gave the title compound (39 mg, 61%) as white solid. MS m/e: 505 ([M+H]^+)
Example 42

trans-8-Fluoro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzolo][azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white solid in 60% yield according to general procedure (X).

Hydrazide: in n5-4-(3-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Fluoro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 482 ([M+H]+)

Example 43

trans-8-Fluoro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzolo][azulene

The title compound was obtained as white solid in 76% yield from ia n5-8-fluoro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure (XI-b). MS m/e: 398 ([M+H]+)

Example 44

trans-8-Fluoro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzolo][azulene

The title compound was obtained as white solid in 46% yield from ia n5-8-fluoro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 396 ([M+H]+)

Example 45

ds-8-Chloro-l-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzolo][azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as off-white solid in 51% yield according to general procedure (X).

Hydrazide: cis in n5-4-(3-Fluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide (7.8:1)

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 498 ([M+H]+)

Example 46
The title compound was obtained as off-white solid in 78% yield from cis-8-chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure (XI-b). MS m/e: 398 ([M+H]+)

Example 47

cis-8-Chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H,2,3,5,10b-tetraaza-benzo[e]azulene

The title compound was obtained as off-white solid in 78% yield from cis-8-chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure (XI-b). MS m/e: 398 ([M+H]+)

Example 48

trans-8-Chloro-1-(4-pyridin-3-yl-cyclohexyl)-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white solid in 88% yield from cis-8-chloro-1-[4-(3-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H,2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 412 ([M+H]+)

Example 49

trans-8-Chloro-1-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4 H,2,3,5,10b-tetraaza-benzo[e]azulene

The title compound was obtained as light yellow solid in 81% yield according to general procedure (X).

Hydrazide: in nN-4-Pyridin-3-yl-cyclohexanecarboxylic acid hydrazide
Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 480 ([M+H]+)

Example 50

trans-8-Chloro-5-methyl-1-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4 H,2,3,5,10b-tetraaza-benzo[e]azulene

The title compound was obtained as light yellow solid in 94% yield from trans-8-chloro-1-(4-pyridin-3-yl-cyclohexyl)-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure (XI-a). MS m/e: 380 ([M+H]+)

Example 50

trans-8-Chloro-5-methyl-1-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4 H,2,3,5,10b-tetraaza-benzo[e]azulene
The title compound was obtained as white solid in 88% yield from \( nS \)-8-chloro-1-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4 \( H \)-2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 394 ([M+H]+)

**Example 51**

**trans-8-Chloro-1-[4-(2-chloro-pyridin-3-yl)-cyclohexyl]-4 \( H \),6\( H \)-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester**

The title compound was obtained as light yellow solid in 84% yield according to general procedure (X).

Hydrazide: \( nS \)-4-(2-Chloro-pyridin-3-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 514 ([M+H]+)

**Example 52**

**trans-8-Chloro-1-[4-(2-chloro-pyridin-3-yl)-cyclohexyl]-5,6-dihydro-4 \( H \)-2,3,5,10b-tetraaza-benzo[e]azulene**

The title compound was obtained as off-white solid in 98% yield from \( nS \)-8-chloro-1-[4-(2-chloro-pyridin-3-yl)-cyclohexyl]-4 \( H \),6\( H \)-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure (XI-b). MS m/e: 414 ([M+H]+)

**Example 53**

**trans-8-Chloro-1-[4-(2-fluoro-pyridin-3-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 \( H \)-2,3,5,10b-tetraaza-benzo[e]azulene**

The title compound was obtained as white solid in 50% yield from \( nS \)-8-chloro-1-[4-(2-fluoro-pyridin-3-yl)-cyclohexyl]-5,6-dihydro-4 \( H \)-2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 428 ([M+H]+)

**Example 54**

**trans-8-Chloro-1-[4-(2-fluoro-pyridin-3-yl)-cyclohexyl]-4 \( H \),6\( H \)-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester**

The title compound was obtained as yellow solid in 65% yield according to general procedure (X).

Hydrazide: \( nS \)-4-(2-Fluoro-pyridin-3-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-
Example 55

**trans-8-Chloro-1-[4-(2-fluoro^yridin-3-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo]>azulene**

The title compound was obtained as yellow solid in quantitative yield from \( nS \)-8-chloro-1-[4-(2-fluoro-pyridin-3-yl)-cyclohexyl]-4 \( H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester** according to general procedure (XI-b). MS m/e: 398 ([M+H]+)

Example 56

**trans-8-Chloro-1-[4-(2-fluoro^yridin-3-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo]>azulene**

The title compound was obtained as white solid in 53% yield from \( nS \)-8-chloro-1-[4-(2-fluoro-pyridin-3-yl)-cyclohexyl]-5,6-dihydro-4 \( H-2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 412 ([M+H]+)

Example 57

**trans-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester**

and

Example 58

**c/s-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester**

in \( nS \)-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-4 \( H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester and cis-8-chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-4 \( H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester were obtained according to general procedure (X) after chromatographic separation.

Hydrazide: cisisin \( nS \)-4-Pyrimidin-2-yl-cyclohexane carboxylic acid hydrazide
Thiolactam: 7-Chloro-2-thiox- 1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid tert-butyl ester

in \( nS \)-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-4 \( H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid ieri-butyl ester was obtained as white solid in 19% yield. MS m/e: 481 ([M+H]+)
d5'-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-4 \( H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester was obtained as white solid in 36% yield. MS m/e: 481 ([M+H]+)
Example 59

\textit{trans-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[\textgreater]azulene}

The title compound was obtained as white solid in quantitative yield from \textit{trans-8-chloro-1-(4-pyrimidin-2-yl-cyclohexyl)}-4 \textit{H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester} according to general procedure (XI-a). MS m/e: 381 ([M+H]+)

Example 60

\textit{trans-8-Chloro-5-methyl-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[\textgreater]azulene}

The title compound was obtained as white solid in 77% yield from \textit{trans-8-chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene} and \textit{paraformaldehyde} according to general procedure (XII). MS m/e: 395 ([M+H]+)

Example 61

\textit{ds-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[\textgreater]azulene}

The title compound was obtained as white solid in 95% yield from \textit{cis-8-chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester} according to general procedure (XI-a). MS m/e: 381 ([M+H]+)

Example 62

\textit{ds-8-Chloro-5-methyl-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[\textgreater]azulene}

The title compound was obtained as white solid in 21% yield from \textit{cis-8-chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene} and \textit{paraformaldehyde} according to general procedure (XII). MS m/e: 395 ([M+H]+)

Example 63

\textit{trans-8-Chloro-1-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[\textgreater]azulene-5-carboxylic acid tert-butyl ester}

The title compound was obtained as white solid in 70% yield according to general procedure (X). Hydrazide: in \textit{nS-4-(4,6-Dimethyl-pyrimidin-2-yl)-cyclohexanecarboxylic acid hydrazide}

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-
butyl ester
MS m/e: 509 ([M+H]+)

Example 64

trans-8-Chloro-l-[4-(4,6-dimethylpyrimidin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride

The title compound was obtained as off-white solid in quantitative yield from iraw^-S-chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester according to general procedure (ΧΙ-a). MS m/e: 409 ([M+H]+)

Example 65

trans-8-Chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene

The title compound was obtained as white solid in 62% yield from iraw^-S-chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure (ΧΙΙ). MS m/e: 423 ([M+H]+)

Example 66

trans-8-Chloro-l-[4-(2-methyl-pyrimidin-4-yl)-cyclohexyl]-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white solid in 61% yield according to general procedure (Χ). Hydrazide: in iraw^-S-(2-Methyl-pyrimidin-4-yl)-cyclohexanecarboxylic acid hydrazide
Thiolactam: 7-Chloro-2-thioxo- 1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid tert-butyl ester
MS m/e: 495 ([M+H]+)

Example 67

trans-8-Chloro-l-[4-(2-methyl-pyrimidin-4-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene

The title compound was obtained as off-white solid in quantitative yield from iraw^-S-chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester according to general procedure (ΧΙ-a). MS m/e: 395 ([M+H]+)

Example 68
trans-8-Chloro-5-methyl-1-[4-(2-methyl-pyrimidin-4-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

The title compound was obtained as white solid in 83% yield from 8-chloro-l-[4-(2-methyl-pyrimidin-4-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 409 ([M+H]⁺)

Example 69

trans-8-Chloro-l-(4-pyrazin-2-yl-cyclohexyl)-4 H,6H-2,3,5,10b-tetraaza-benzo[>]azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as light brown solid in 41% yield according to general procedure (X).

Hydrazide: in 8-(Pyrazin-2-yl)-cyclohexanecarboxylic acid hydrazide
Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[1,4]diazepine-4-carboxylic acid tert-butyl ester
MS m/e: 481 ([M+H]⁺)

Example 70

trans-8-Chloro-l-(4-pyrazin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

The title compound was obtained as yellow solid in 83% yield from in 8-chloro-l-(4-pyrazin-2-yl-cyclohexyl)-4 H,6H-2,3,5,10b-tetraaza-benzo[>]azulene-5-carboxylic acid tert-butyl ester according to general procedure (XI-a). MS m/e: 381 ([M+H]⁺)

Example 71

trans-8-Chloro-5-methyl-l-(4-pyrazin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

The title compound was obtained as white solid in 59% yield from in 8-chloro-l-(4-pyrazin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 395 ([M+H]⁺)

Example 72

trans-8-Chloro-l-[4-(6-methyl-pyrazin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[>]azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white solid in 73% yield according to general procedure (X).

Hydrazide: in 8-(6-Methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid hydrazide
Example 73

**trans-8-Chloro-1-[4-(6-methylpyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H-2,3,5,10b \)-tetraaza-benzoazulene**

The title compound was obtained as white solid in quantitative yield from \( \text{nS-8-chloro-1-[4-(6-methyl-pyrazin-2-yl)-cyclohexyl]-4 \( H.6H \)-2,3,5,10b-tetraaza-benzo[\text{e}]azulene-5-carboxylic acid tert-butyl ester} \) according to general procedure (XI-a). MS m/e: 395 ([M+H]+)

Example 74

**trans-8-Chloro-5-methyl-1-[4-(6-methyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H-2,3,5,10b \)-tetraaza-benzoazulene**

The title compound was obtained as white solid in 76% yield from \( \text{nS-8-chloro-1-[4-(6-methyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H.2,3,5,10b \)-tetraaza-benzo[\text{e}]azulene-5-carboxylic acid tert-butyl ester} \) and paraformaldehyde according to general procedure (XII). MS m/e: 409 ([M+H]+)

Example 75

**trans-8-Chloro-1-[4-(3-methyl-pyrazin-2-yl)-cyclohexyl]-4 \( H.6H \)-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester**

The title compound was obtained as light yellow solid in 50% yield according to general procedure (X).

Hydrazide: in \( \text{nS-4-(3-Methyl-pyrazin-2-yl)-cyclohexanecarboxylic acid hydrazide} \)

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[\text{e}] [1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 495 ([M+H]+)

Example 76

**trans-8-Chloro-1-[4-(3-methyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H-2,3,5,10b \)-tetraaza-benzoazulene**

The title compound was obtained as yellow solid in quantitative yield from \( \text{nS-8-chloro-1-[4-(3-methyl-pyrazin-2-yl)-cyclohexyl]-4 \( H.6H \)-2,3,5,10b-tetraaza-benzo[\text{e}]azulene-5-carboxylic acid tert-butyl ester} \) according to general procedure (XI-a). MS m/e: 395 ([M+H]+)

Example 77
trans-8-Chloro-5-methyl-1-[4-(3-methyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

The title compound was obtained as white solid in 59% yield from 1S-8-chloro-1-[4-(3-methyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 409 ([M+H]+)

Example 78

trans-8-Chloro-1-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[>]azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as light yellow solid in 72% yield according to general procedure (X).

Hydrazide: in 1S-4-(3,6-Dimethyl-pyrazin-2-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 509 ([M+H]+)

Example 79

trans-8-Chloro-1-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene hydrochloride

The title compound was obtained as light yellow solid in quantitative yield from iraw-8-chloro-1-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester according to general procedure (XI-a). MS m/e: 409 ([M+H]+)

Example 80

trans-8-Chloro-1-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

The title compound was obtained as white solid in 24% yield from 1S-8-chloro-1-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure (XII). MS m/e: 423 ([M+H]+)

Example 81

trans-8-Chloro-5-methyl-1-(4-pyridazin-3-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

trans-8-Chloro-5-methyl-1-[4-(3-methyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[>]azulene

The title compound was obtained as white solid in 59% yield from 1S-8-chloro-1-[4-(3-methyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure (XII). MS m/e: 409 ([M+H]+)
The title compound was obtained as off-white solid in 59% yield according to general procedure (X).

Hydrazide: \textit{cis} in \textit{ns}-4-Pyridazin-3-yl-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid \textit{tert}-butyl ester

MS m/e: 481 ([M+H]+)

The title compound was obtained as light yellow solid in quantitative yield from \textit{cw} in \textit{ns}-8-chloro-l-(4-pyridazin-3-yl-cyclohexyl)-4 \textit{H}-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid \textit{tert}-butyl ester according to general procedure (XI-a). MS m/e: 381 ([M+H]+)

c) \textit{trans}-8-Chloro-5-methyl-l-(4-pyridazin-3-yl-cyclohexyl)-5,6-dihydro-4 \textit{H}-2,3,5JOb-tetraaza-

benzoTelazulene hydrochloride

The title compound was obtained as light yellow solid in 15% yield from \textit{ds} in \textit{ns}-8-chloro-l-(4-pyridazin-3-yl-cyclohexyl)-5,6-dihydro-4 \textit{H}-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure (XII). MS m/e: 395 ([M+H]+)

Example 82

\textit{trans}-8-Chloro-l-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-4\textit{H},6\textit{H}-2,3,5,10b-tetraaza-

benzo[e]azulene-5-carboxylic acid \textit{tert}-butyl ester

The title compound was obtained as white solid in 70% yield according to general procedure (X). Hydrazide: in \textit{ns}-4-(3-Chloro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e] [1,4]diazepine-4-carboxylic acid \textit{tert}-butyl ester

MS m/c: 514 ([M+H]+)

Example 83

\textit{trans}-8-Chloro-l-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4\textit{H}-2,3,5,10b-tetraaza-

benzo[e]azulene
The title compound was obtained as white solid in 99% yield from nitro-8-chloro-l-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure (XIII). MS m/e: 414 ([M+H]+)

Example 84

5 trans-8-Chloro-l-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene

The title compound was obtained as white solid in 83% yield from nitro-8-chloro-l-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene according to general procedure (XIII). MS m/e: 428 ([M+H]+)

Example 85

6 trans-8-Chloro-l-[4-(3,5-difluoro-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white solid in 76% yield according to general procedure (X). Hydrazide: in nitro-4-(3,5-Difluoro-pyridin-2-yl)-cyclohexanecarboxylic acid hydrazide

Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester

MS m/e: 516 ([M+H]+)

Example 86

20 trans-8-Chloro-l-[4-(3,5-difluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene

The title compound was obtained as white solid in quantitative yield from nitro-8-chloro-l-[4-(3,5-difluoro-pyridin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure (XI-b). MS m/e: 416 ([M+H]+)

Example 87

25 trans-8-Chloro-l-[4-(3,5-difluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene

The title compound was obtained as white solid in 72% yield from nitro-8-chloro-l-[4-(3,5-difluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene according to general procedure (XIII). MS m/e: 430 ([M+H]+)
Claims

1. A compound of the formula I

wherein

5  $R^1$ is selected from the group consisting of

i)  $H$,

ii)  -$Ci$-$6$-$alkyl$, unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of $OH$, halogen, cyano and $Ci$-$6$-$alkoxy$,

iii)  -$S(0)_2$-$C_1$-$6$-$alkyl$, wherein the $C_1$-$6$-$alkyl$ is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of $OH$, halogen, cyano and $Ci$-$6$-$alkoxy$,

iv)  -$C(0)$-$C_1$-$6$-$alkyl$, wherein the $Ci$-$6$-$alkyl$ is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of $OH$, halogen, cyano and $Ci$-$6$-$alkoxy$,

v)  -$C(0)$-$C_1$-$6$-$alkyl$, wherein the $Ci$-$6$-$alkyl$ is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of $OH$, halogen, cyano and $Ci$-$6$-$alkoxy$;

vi)  cycloalkyl, unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of $OH$, halogen, cyano, $Ci$-$6$-$alkyl$ and $Ci$-$6$-$alkoxy$;

vii)  $S(0)_2$-$($CH$_2$)$_q$-$NR^i$-$R^i$, wherein

$q$ is 0 or 1.

$R^1$ and $R^i$ is each individually selected from the group consisting of $H$ and $Ci$-$6$-$alkyl$, or $R^1$ and $R^i$ form together with the nitrogen to which they are attached a 3- to 7-membered heterocyclyl containing one or two heteroatoms individually selected from $N$, $O$ and $S$, and which heterocyclyl is unsubstituted or substituted by 1 to 5
substituents individually selected from the group consisting of oxo, halogen, C_{1-6}-alkyl and Ci-6-alkoxy,

viii) \(-(\text{CH}_2)_r\text{NR}^\text{iii}\text{R}^\text{iv}\), wherein

\(r\) is 1, 2 or 3,

\(R^\text{iv}\) and \(R^\text{v}\) is each individually selected from the group consisting of H and Ci-6-alkyl, or \(R^\text{iv}\) and \(R^\text{v}\) form together with the nitrogen to which they are attached a 3- to 7-membered heterocyclyl containing one or two heteroatoms individually selected from N, O and S, and which heterocyclyl is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of oxo, halogen, C_{1-6}-alkyl and Ci-6-alkoxy, and

ix) \(-\text{C(0)}(\text{CH}_2)_s\text{NR}^\text{v}\text{R}^\text{vi}\), wherein

\(s\) is 1, 2 or 3,

\(R^\text{v}\) and \(R^\text{vi}\) is each individually selected from the group consisting of H and Ci-6-alkyl, or \(R^\text{v}\) and \(R^\text{vi}\) form together with the nitrogen to which they are attached a 3- to 7-membered heterocyclyl containing one or two heteroatoms individually selected from N, O and S, and which heterocyclyl is unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of oxo, halogen, C_{1-6}-alkyl and Ci-6-alkoxy;

\(R^2\) is halogen; and

\(R^3\) is a 6-membered heteroaryl ring, unsubstituted or substituted by 1 to 5 substituents individually selected from the group consisting of OH, halogen, cyano, Ci-6-alkyl, Ci-6-alkoxy, halogen-Ci-6-alkyl, halogen-Ci-6-alkoxy and hydroxy-Ci-6-alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein \(R^1\) is selected from the group consisting of

i) \(\text{H}\),

ii) \(-\text{Ci-6-alkyl},\) unsubstituted or substituted by 1 to 2 substituents individually selected from the group consisting of halogen and Ci-6-alkoxy,

iii) \(-\text{S(0)}\_2\text{-C}_{1,6}-\text{alkyl},\) wherein the Ci-6-alkyl is unsubstituted,

iv) \(-\text{C(0)}\_\text{-C}_{1,6}-\text{alkyl},\) wherein the Ci-6-alkyl is unsubstituted or substituted by 1 to 2 OH,

v) \(-\text{C(0)0-C}_{1,6}-\text{alkyl},\) wherein the Ci-6-alkyl is unsubstituted;
vi) unsubstituted cycloalkyl,

vii) \( S(0)_2-(\text{CH}_2)_q-\text{NR}^\text{ii} \), wherein \( q \) is 0,

\( R^1 \) and \( R^\text{ii} \) is each individually selected from the group consisting of \( H \) and \( \text{C}_1-\text{C}_6\text{-alkyl} \), and

viii) \( -(\text{CH}_2)_r-\text{NR}^\text{iii} \text{R}^\text{iv} \), wherein \( r \) is 2,

\( R^\text{iii} \) and \( R^\text{iv} \) is each individually selected from the group consisting of \( H \) and \( \text{C}_1-\text{C}_6\text{-alkyl} \), and

ix) \( -\text{C}(\text{O})(\text{CH}_2)_s-\text{NR}^\text{v} \text{R}^\text{vi} \), wherein \( s \) is 1.

\( R^\text{v} \) and \( R^\text{vi} \) is each individually selected from the group consisting of \( H \) and \( \text{C}_1-\text{C}_6\text{-alkyl} \).

3. A compound according to any of claims 1-2, wherein \( R^1 \) is selected from the group consisting of

i) \( H \),

ii) \(-\text{C}_1-\text{C}_6\text{-alkyl}, unsubstituted or substituted by 1 to 2 substituents individually selected from the group consisting of halogen and \( \text{C}_1-\text{C}_6\text{-alkoxy} \), and

iii) unsubstituted cycloalkyl.

4. A compound according to any of claims 1-3, wherein \( R^1 \) is selected from the group consisting of \( H \), methyl, ethyl, isopropyl, 2,2-difluoroethyl, 2-methoxy-ethyl and cyclobutyl.

5. A compound according to any of claims 1-4, wherein \( R^2 \) is chloro.

6. A compound according to any of claims 1-5, wherein \( R^3 \) is selected from the group consisting of

i) pyridinyl, unsubstituted or substituted by 1 to 2 substituents individually selected from the group consisting of halogen, \( \text{C}_1-\text{C}_6\text{-alkyl} \) and \( \text{C}_1-\text{C}_6\text{-alkoxy} \),

ii) pyrazinyl, unsubstituted or substituted by 1 to 2 \( \text{C}_1-\text{C}_6\text{-alkyl} \),

iii) unsubstituted pyridazinyl, and

iv) pyrimidinyl, unsubstituted or substituted by 1 to 2 \( \text{C}_1-\text{C}_6\text{-alkyl} \).

7. A compound according to any of claims 1-6, wherein \( R^3 \) is
i) pyridinyl, unsubstituted or substituted by 1 to 2 substituents individually selected from the group consisting of halogen and C\textsubscript{6}-alkyl, or

ii) unsubstituted pyrazinyl.

8. A compound according to any of claims 1-7, wherein R\textsuperscript{3} is selected from the group consisting of pyridin-2-yl, 6-methyl-pyridin-2-yl, 3-chloro-pyridin-2-yl, 3,5-difluoro-pyridin-2-yl, 6-chloro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 3-fluoro-pyridin-2-yl and pyrazin-2-yl.

9. A compound according to any of claims 1-8, wherein R\textsuperscript{3} is selected from the group consisting of pyridin-2-yl, 6-methyl-pyridin-2-yl, 6-chloro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 3-fluoro-pyridin-2-yl and pyrazin-2-yl.

10. A compound according to any of claims 1-9, selected from the group consisting of

\textit{in d5'-8-Chloro-l-(4-pyridin-2-yl-cyclohexyl)-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester,}

in \textit{ns'-8-Chloro-l-(4-pyridin-2-yl-cyclohexyl)-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester,}

\textit{in ns'-8-Chloro-l-(4-pyrimidin-2-yl-cyclohexyl)-4 H.6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester,}

\textit{in ns'-8-Chloro-l-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene,}

\textit{in ns'-8-Chloro-5-methyl-l-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene,}

\textit{1-(irara-8-chloro-l-((IR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 H)-yl)ethanone,}

\textit{1-(irara-8-chloro-l-((IR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 H)-yl)-2-hydroxyethanone,}

\textit{1-(irara-8-chloro-l-((IR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 H)-yl)-2-(dimethylamino)ethanone formate,}

\textit{2-(irara-8-chloro-l-((IR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 H)-yl)-N-methylethanamine,}


\textit{iw5'-8-Chloro-l-[4-(3,5-difluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene,}

\textit{iw5'-8-Chloro-l-[4-(3,5-difluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene,}
in \textit{nS}-8-Chloro-1-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 \textit{H}-2,3,5,10b-tetraaza-benz[e]azulene, \\
\textit{nS}-8-Chloro-1-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-4 \textit{H},.6\textit{H}-2,3,5,10b-tetraaza-benz[e]azulene-5-carboxylic acid tert-butyl ester, \\
\textit{nms}-8-Chloro-1-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \textit{H}-2,3,5,10b-tetraaza-benz[e]azulene, \\
\textit{dS}'-8-chloro-1-((1S,4R)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
cis-8-Chloro-1-((1S,4R)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
cis-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
cis-8-Chloro-5-methyl-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
cis-Iter-\textit{I}(\textit{I}R,4\textit{R})-4-(3-fluoropyridin-2-yl)cyclohexyl]-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{R})-4-(3-methylpyrimidin-4-yl)cyclohexyl]-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(3-fluoropyridin-2-yl)cyclohexyl]-5-(2-methoxyethyl)-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(3-fluoropyridin-2-yl)cyclohexyl]-5-(methylsulfonyl)-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(3-fluoropyridin-2-yl)cyclohexyl]-5-isopropyl-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(4-chloropyridin-2-yl)cyclohexyl]-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(4-chloropyridin-2-yl)cyclohexyl]-5-methyl-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(2-chloropyridin-3-yl)cyclohexyl]-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(2-chloropyridin-3-yl)cyclohexyl]-5-methyl-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(2-methylpyrimidin-4-yl)cyclohexyl]-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(3-fluoropyridin-2-yl)cyclohexyl]-5-(2-methoxyethyl)-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(3-fluoropyridin-2-yl)cyclohexyl]-5-(methylsulfonyl)-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(3-fluoropyridin-2-yl)cyclohexyl]-5-isopropyl-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(4-chloropyridin-2-yl)cyclohexyl]-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
\textit{I}(\textit{I}R,4\textit{S})-4-(4-chloropyridin-2-yl)cyclohexyl]-5-methyl-5,6-dihydro-4 \textit{H}-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, \\
in \textit{nS}-8-Chloro-1-[4-(3-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \textit{H}-2,3,5,10b-tetraaza-benz[e]azulene.
in \( \text{ns-8-chloro-l-[(lR,4S)-4-(6-fluoropyridin-2-yl)cyclohexyl]-5,6-dihydro-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine} \), in \( \text{ns-8-chloro-l-[(lR,4S)-4-(6-fluoropyridin-2-yl)cyclohexyl]-5-methyl-5,6-dihydro-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine} \),

5 \( \text{trans-8-Chloro-l-(4-pyrazin-2-yl-cyclohexyl)-4 H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester} \), in \( \text{ns-8-Chloro-l-(4-pyrazin-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-(4-pyrazin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-(4-pyridin-3-yl-cyclohexyl)-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5-carboxylic acid tert-butyl ester} \), in \( \text{ns-8-Chloro-l-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5-carboxylic acid tert-butyl ester} \), in \( \text{ns-8-Chloro-l-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(3,6-dimethyl-pyrazin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5-carboxylic acid tert-butyl ester} \), in \( \text{ns-8-Chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5-carboxylic acid tert-butyl ester} \), in \( \text{ns-8-Chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-carboxylic acid tert-butyl ester} \), in \( \text{ns-8-Chloro-l-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns-8-Chloro-l-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5-carboxylic acid tert-butyl ester} \), in \( \text{ns-8-Chloro-l-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene} \),
in \( \text{ns} \)-8-Chloro-l-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H \)-2,3,5,10b-tetraaza-benzo[\( e \)]azulene,

in \( \text{ns} \)-8-Chloro-l-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 \( H \)-2,3,5,10b-tetraaza-benzo[\( e \)]azulene,

\( \text{trans} \)-8-Chloro-l-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-4 \( H \)-2,3,5,10b-tetraaza-benzo[\( e \)]azulene-5-carboxylic acid \( \text{tert} \)-butyl ester,

in \( \text{ns} \)-8-Chloro-l-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H \)-2,3,5,10b-tetraaza-benzo[\( e \)]azulene,

in \( \text{ns} \)-8-Chloro-l-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 \( H \)-2,3,5,10b-tetraaza-benzo[\( e \)]azulene,

in \( \text{ns} \)-8-Chloro-l-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-4 \( H \)-2,3,5,10b-tetraaza-benzo[\( e \)]azulene-hydrochloride,

in \( \text{ns} \)-8-Chloro-l-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H \)-2,3,5,10b-tetraaza-benzo[\( e \)]azulene,

in \( \text{ns} \)-8-Chloro-l-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-4 \( H \)-2,3,5,10b-tetraaza-benzo[\( e \)]azulene,

in \( \text{ns} \)-8-Chloro-l-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( H \)-2,3,5,10b-tetraaza-benzo[\( e \)]azulene,

in \( \text{ns} \)-8-Chloro-l-[4-(6-methyl-pyrazin-2-yl)-cyclohexyl]-4 \( H \)-2,3,5,10b-tetraaza-benzo[\( e \)]azulene,

in \( \text{ns} \)-8-chloro-5-(2,2-difluoroethyl)-l-((1R,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 \( H \)-benzo[\( e \)][1,2,4]triazolo[4,3-a][1,4]diazepine,

in \( \text{ns} \)-8-chloro-5-cyclobutyl-l-((1R,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 \( H \)-benzo[\( e \)][1,2,4]triazolo[4,3-a][1,4]diazepine,

in \( \text{ns} \)-8-chloro-5-ethyl-l-((1R,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 \( H \)-benzo[\( e \)][1,2,4]triazolo[4,3-a][1,4]diazepine,

in \( \text{ns} \)-8-chloro-5-methyl-l-((1R,4S)-4-(2-methylpyrimidin-4-yl)cyclohexyl)-5,6-dihydro-4 \( H \)-benzo[\( e \)][1,2,4]triazolo[4,3-a][1,4]diazepine,

in \( \text{ns} \)-8-chloro-5-methyl-l-((1R,4S)-4-(3-methylpyrazin-2-yl)cyclohexyl)-5,6-dihydro-4 \( H \)-benzo[\( e \)][1,2,4]triazolo[4,3-a][1,4]diazepine,
in \( \text{n}^8 \)-8-Chloro-5-methyl-1-(4-pyrazin-2-yl-cyclohexyl)-5,6-dihydro-4 \( \text{H} \)-2,3,5,10b-tetraaza-benzo[e]azulene,
in \( \text{n}^8 \)-8-Chloro-5-methyl-1-(4-pyridazin-3-yl-cyclohexyl)-5,6-dihydro-4 \( \text{H} \)-2,3,5,10b-tetraaza-benzo[e]azulene,
in \( \text{n}^8 \)-8-Chloro-5-methyl-1-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4 \( \text{H} \)-2,3,5,10b-tetraaza-benzo[e]azulene,
in \( \text{n}^8 \)-8-Chloro-5-methyl-1-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4 \( \text{H} \)-2,3,5,10b-tetraaza-benzo[e]azulene,
in \( \text{n}^8 \)-8-Chloro-1-[4-(6-methyl-pyrazin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( \text{H} \)-2,3,5,10b-tetraaza-benzo[e]azulene,
in \( \text{n}^8 \)-8-Chloro-1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 \( \text{H} \)-2,3,5,10b-tetraaza-benzo[e]azulene,
in \( \text{n}^8 \)-8-Fluoro-1-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 \( \text{H} \)-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in \( \text{n}^8 \)-8-Fluoro-1-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 \( \text{H} \)-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
\( \text{trans} \)-tert-butyl 8-chloro-1-((lR,4R)-4-(2-fluoropyridin-3-yl)cyclohexyl)-4 \( \text{H} \)-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6 \( \text{H} \))-carboxylate,
\( \text{trans} \)-tert-butyl 8-chloro-1-((lR,4S)-4-(2-chloropyridin-3-yl)cyclohexyl)-4 \( \text{H} \)-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6 \( \text{H} \))-carboxylate,
\( \text{trans} \)-tert-butyl 8-chloro-1-((lR,4S)-4-(2-methylpyrimidin-4-yl)cyclohexyl)-4 \( \text{H} \)-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6 \( \text{H} \))-carboxylate,
\( \text{trans} \)-tert-butyl 8-chloro-1-((lR,4S)-4-(3-methylpyrazin-2-yl)cyclohexyl)-4 \( \text{H} \)-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6 \( \text{H} \))-carboxylate,
\( \text{trans} \)-tert-butyl 8-chloro-1-((lR,4S)-4-(4-chloropyridin-2-yl)cyclohexyl)-4 \( \text{H} \)-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6 \( \text{H} \))-carboxylate,
\( \text{trans} \)-tert-butyl 8-fluoro-1-((lR,4S)-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 \( \text{H} \)-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6 \( \text{H} \))-carboxylate,
or a pharmaceutically acceptable salt thereof.

11. A compound according to any of claims 1-10, selected from the group consisting of

in \( \text{n}^8 \)-8-Chloro-1-(4-pyridin-2-yl-cyclohexyl)-4 \( \text{H} \)-6 \( \text{H} \)-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid iert-butyl ester,
in \( \text{n}^8 \)-8-Chloro-1-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4 \( \text{H} \)-2,3,5,10b-tetraaza-benzo[e]azulene,
in **8-Chloro-1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid tert-butyl ester,**
in **8-Chloro-1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzo[e]azulene,**
5 in **8-Chloro-5-methyl-1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzo[e]azulene,**
in **8-Chloro-1-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid tert-butyl ester,**
in **8-Chloro-1-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzo[e]azulene,**
10 in **8-Chloro-1-[4-(6-ethyl-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzo[e]azulene,**
in **8-Chloro-1-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid iert-butyl ester,**
in **8-Chloro-1-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzo[e]azulene hydrochloride,**
in **8-Chloro-1-[4-(6-isopropyl-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzo[e]azulene,**
in **8-Chloro-1-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid tert-butyl ester,**
in **8-Chloro-1-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzo[e]azulene,**
in **8-Chloro-1-[4-(6-methoxy-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-
tetraaza-benzoazulene,**
20 in **8-Chloro-1-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzo[e]azulene,**
in **8-Chloro-1-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-
tetraaza-benzoazulene,**
in **8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid tert-butyl ester,**
in **8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzo[e]azulene,**
in **8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-
tetraaza-benzo[e]azulene,**

trans-**8-Chloro-1-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid iert-butyl ester,**
in **8-Chloro-1-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzo[e]azulene,**
in **8-Chloro-1-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-
tetraaza-benzo[e]azulene,**

**trans-tert-Butyl 8-chloro-1-(-4-(6-fluoropyridin-2-yl)cyclohexyl)-4 H-
benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6 H)-carboxylate,**
in **8-Chloro-1-(-4-(6-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4 H-
benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,**
35 in **8-Chloro-1-(-4-(6-fluoropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 H-
benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,**
in **8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-4 H,6H-2,3,5,10b-tetraaza-
benzoaazulene-5-carboxylic acid tert-butyl ester,**
in **8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4 H-2,3,5,10b-tetraaza-
benzoaazulene,**
in 8-Chloro-l-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzoazulene,

trans-tert-Butyl 8-chloro-l-(-4-(4-chloropyridin-2-yl)cyclohexyl)-4 H-benzo[e][1,2,4]triazolo[4,3-a] [1,4]diazepine-5(6 H)-carboxylate,

in 8-Chloro-l-(-4-(4-chloropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

in 8-Chloro-l-(-4-(4-chloropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

in 8-Chloro-l-(-4-(4-chloropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

in 8-Chloro-l-(-4-(4-chloropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,

in 8-Chloro-l-[-4-(3-fluoropyridin-2-yl)cyclohexyl]-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 H)-yl)-N-methylethanamine,

l-(8-Chloro-l-(-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 H)-yl)ethanone,

2-(8-Chloro-l-(-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 H)-yl)-2-hydroxyethanone,

1-(8-Chloro-l-(-4-(3-fluoropyridin-2-yl)cyclohexyl)-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepin-5(6 H)-yl)ethanone,

in 8-Chloro-l-(-4-(3-fluoropyridin-2-yl)cyclohexyl)-5-(methylsulfonyl)-5,6-dihydro-4 H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
-8-Fluoro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
cis-tert-Butyl 8-chloro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine-5(6H)-carboxylate,
cis-8-Chloro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
cis-8-Chloro-1-(4-pyridin-3-yl-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in ns-8-Chloro-1-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-5-methyl-1-(4-pyridin-3-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
in ns-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-5-methyl-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-1-(4-pyrimidin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in ns-8-Chloro-1-[4-(4,6-dimethyl-pyrimidin-2-yl)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
5. **trans-tert-Butyl** 8-chloro-l-(-4-(2-methylpyrimidin-4-yl)cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[ε]azulene-5-carboxylic acid tert-butyl ester,
in ns-8-Chloro-l-(-4-(2-methylpyrimidin-4-yl)cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[ε]azulene,
in ira-S-Chloro-S-methyl-l-(4-pyrain-2-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[ε]azulene,
in ns-8-Chloro-l-(-4-(3-methylpyrazin-2-yl)cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[ε]azulene,
in trans-tert-Butyl 8-chloro-l-(4-(3,6-dimethyl-pyrazin-2-yl)cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[ε]azulene-5-carboxylic acid iert-butyl ester,
in ns-8-Chloro-l-(-4-(3,6-dimethyl-pyrazin-2-yl)cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[ε]azulene,
in ns-8-Chloro-l-(-4-(3-pyridazin-3-yl-cyclohexyl)-5,6-dihydro-4 H-2,3,5,10b-tetraaza-benzo[ε]azulene,
or a pharmaceutically acceptable salt thereof.

12. A compound according to any of claims 1-11, selected from the group consisting of
in 8-Chloro-l-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzo[e]azulene *2 HCl,
in 8-Chloro-5-methyl-l-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzo[e]azulene,
in 8-Chloro-5-(2,2-difluoroethyl)-l-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-
benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-l-(4-(5-fluoro-3-pyridin-2-yl)cyclohexyl)-5-methyl-5,6-dihydro-4H-
benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-5-methyl-1-(4-pyridin-2-yl-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-5-methyl-1-[4-(6-methyl-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,

**trans**-8-Chloro-1-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-[4-(6-chloro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene dihydrochloride,
in 8-Chloro-1-[4-(5-fluoro-pyridin-2-yl)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-[4-(3-fluoropyridin-2-yl)cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
in 8-Chloro-1-[4-(3-fluoropyridin-2-yl)cyclohexyl]-5-isopropyl-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5-cyclobutyl-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5-(2,2-difluoroethyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-5-(2,2-difluoroethyl)-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine,
in 8-Chloro-1-(4-(3-fluoropyridin-2-yl)cyclohexyl)-5-(2-methoxyethyl)-5,6-dihydro-4H-benzo[e][1,2,4]triazolo[4,3-a][1,4]diazepine, and

**14.** A process for the preparation of the compound of formula I according to any of claims 1-13, comprising the step of reacting a compound of formula II

![Chemical Structure](https://example.com/chemical-structure.png)

with a compound of formula III
to obtain a compound of formula I wherein $R^1$, $R^2$ and $R^3$ are as defined in claim 1.

15. A compound formula I, whenever obtained by the process according to claim 14.

16. A compound of formula I according to any one of claims 1-13 for use as therapeutically active substance.

17. A compound of formula I according to any one of claims 1-13 for a use in the prevention or treatment of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

18. A pharmaceutical composition comprising a compound of formula I according to any one of claims 1-13.

19. A pharmaceutical composition according to claims 1-13, wherein it is useful for the prevention or treatment of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

20. Use of a compound of formula I according to any one of claims 1-13 for the preparation of a medicament for the prevention or treatment of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

21. A method for the therapeutic and/or prophylactic treatment of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior, which method comprises administering a compound according to any of claims 1-13 to a human being or animal.

22. The invention as described hereinabove.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/5517 A61P5/24
ADD.

According to International Patent Classification (IPC) and/or both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>A</td>
<td>wo 2006/021882 AI (PFIZER LTD [GB] ; PFIZER [US] ; JOHNSON PATRICK STEPHEN [GB]) 2 March 2006 (2006-03-02) claims ; examples 1-3, 9 ; table 2</td>
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Date of the actual completion of the international search

6 May 2011

Date of mailing of the international search report

12/05/2011

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Authorized officer
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