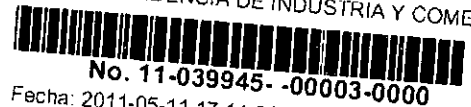


JOSE LLORED A CAMACHO & CO.

ABOGADOS

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-039945- -00003-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 53

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: PI.-F. HOFFMANN-LA ROCHE AG.-Solicitud de Patente de Invención
en Fase Nacional PCT para "ARILCICLOHEXILÉTERES DE
DIHIDRO-TETRAAZABENZOAZULENOS PARA SU USO COMO
ANTAGONISTAS DEL RECEPTOR V1A DE VASOPRESINA".-Clase
C07D 487/04.-Expediente número 11-039.945.-

1. Me refiero a mi memorial de 25 de Abril de 2011.
2. Atentamente me permito presentar a ese Despacho copia debidamente certificada de la Solicitud de Patente **respecto de la cual reclamo prioridad**, dentro del trámite de la Solicitud arriba referida, a saber, la Solicitud Europea número **08170188.0** de 28 de Noviembre de 2008, junto con su Traducción Oficial número 2011-05-05-285, correspondiente a dicho documento.
3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

ALICIA LLORED A RICAURTE

T.P. 53.215

TRADUCCION OFICIAL No. 2011-05-05-285
DE UN DOCUMENTO ESCRITO EN INGLÉS

Certificado

Los documentos adjuntos son copias exactas
de la solicitud de patente europea descrita en
la siguiente página, como se presentó
originalmente.

Solicitud de patente No.

08170188.0 / EP08170188

El código y número de la organización de su solicitud de prioridad, que se usará
para presentación en el exterior bajo la Convención de París es, EP08170188

Por el Presidente de la Oficina
Europea de Patentes
(firma: ilegible)
R.C. van Dijk

Solicitud no.: 08170188

Fecha de presentación: 28.11.08

Solicitante(s):

F. Hoffmann-La Roche AG
Grenzacherstrasse 124
4070 Basel/CH

Si no se muestra ningún título, por favor refiérase a la descripción.

Arilciclohexiléteres de dihidro-tetraazabenzozulenos

Prioridad reivindicada

Estado/Fecha /Archivo no.

Clasificación Internacional de Patentes:

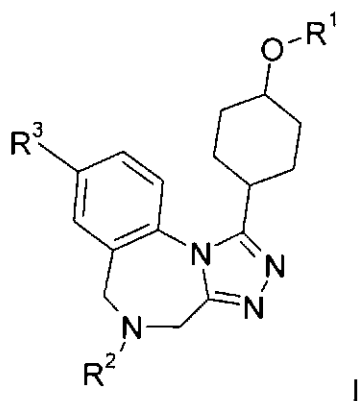
C07D487/00

Estados contratantes designados en la fecha de presentación:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI
LT LU LV MC MT NL NO PL PT RO SE SI SK TR

REIVINDICACIONES

1. El compuesto de la fórmula general I



en la que

R^1 es arilo o heteroarilo, sin sustituir o sustituido por uno o más sustituyentes elegidos con independencia entre A;

R^2 es H,

alquilo C_{1-12} , sin sustituir o sustituido por uno o más OH, halógeno, ciano o alcoxi C_{1-12} ,

$-(CH_2)_q-R^a$, en el que R^a es fenilo o un heteroarilo de 5 ó 6 miembros, cada uno de ellos está sin sustituir o sustituido por uno o más sustituyentes elegidos con independencia entre A,

$-(CH_2)_rNR^iR^{ii}$,

$-C(O)$ -alquilo C_{1-12} , dicho alquilo C_{1-12} está sin sustituir o sustituido por uno o más OH, halógeno, ciano o alcoxi C_{1-12} ,

$-C(O)(CH_2)_qOC(O)$ -alquilo C_{1-12} ,

$-C(O)(CH_2)_qNR^iR^{ii}$,

-C(O)O-alquilo C₁₋₁₂, dicho alquilo está sin sustituir o sustituido por uno o más OH, halógeno, ciano o alcoxi C₁₋₁₂,

-S(O)₂-alquilo C₁₋₁₂,

-S(O)₂NRⁱRⁱⁱ,

Rⁱ y Rⁱⁱ con independencia entre sí son H, alquilo C₁₋₁₂, o junto con el nitrógeno, al que están unidos, forman un heterocicloalquilo de 3 a 7 miembros que contiene uno o dos heteroátomos elegidos entre N, O y S, dicho heterocicloalquilo está sin sustituir o sustituido por uno o más sustituyentes elegidos con independencia entre B,

q es el número 1, 2, 3 ó 4,

r es el número 2, 3 ó 4,

A es halógeno, ciano, OH, alquilo C₁₋₇, halo-alquilo C₁₋₇, alcoxi C₁₋₇, halo-alcoxi C₁₋₇ o hidroxi-alquilo C₁₋₇,

B es oxo, halógeno, OH, alquilo C₁₋₇ o alcoxi C₁₋₇,

R³ es Cl o F,

o una sal farmacéuticamente aceptable del mismo.

2. El compuesto de la fórmula I según la reivindicación 1, en la que

R¹ es un resto hidrocarburo aromático cíclico monovalente formado por un anillo aromático mono- o bicíclico,

un anillo aromático monocíclico monovalente de 5 ó 6 miembros o aromático bicíclico monovalente de 9 ó 10 miembros que contiene de uno a cuatro heteroátomos en el anillo, elegidos entre N, O y S, los demás átomos del anillo son C,

cada uno de ellos está sin sustituir o sustituido por uno o más sustituyentes elegidos con independencia entre A; y

A es halógeno, ciano, OH, alquilo C₁₋₇, halo-alquilo C₁₋₇, alcoxi C₁₋₇, halo-alcoxi C₁₋₇, hidroxi-alquilo C₁₋₇.

3. El compuesto de la fórmula I según una cualquiera de las reivindicaciones 1 ó 2, en el que Rⁱ es H,

alquilo C₁₋₁₂, sin sustituir o sustituido por uno o más OH,

-(CH₂)_q-R^a, en el que R^a es fenilo o un heteroarilo de 5 ó 6 miembros y q es el número 1, 2, 3 ó 4, con preferencia el 1,

-C(O)-alquilo C₁₋₁₂,

-C(O)(CH₂)_qNRⁱRⁱⁱ, en el que Rⁱ y Rⁱⁱ con independencia entre sí son H o alquilo C₁₋₁₂, con preferencia alquilo C₁₋₁₂, y q es el número 1, 2, 3 ó 4, con preferencia el 1,

-C(O)O-alquilo C₁₋₁₂,

-S(O)₂-alquilo C₁₋₁₂, o

-S(O)₂NRⁱRⁱⁱ, en el que Rⁱ y Rⁱⁱ con independencia entre sí son H o alquilo C₁₋₁₂, con preferencia alquilo C₁₋₁₂.

4. El compuesto según una cualquiera de las reivindicaciones 1 a 3, en el que R³ es Cl..

5. El compuesto según una cualquiera de las reivindicaciones 1 a 4, en el que el compuesto es seleccionado de

trans-8-cloro-1-(4-fenoxi-ciclohexil)-4H,6H-2,3,5,10b-tetraaza-
benzoazuleno-5-carboxilato de tert-butilo,

trans-8-cloro-1-(4-fenoxi-ciclohexil)-5,6-dihidro-4H-2,3,5,10b-tetraaza-
benzoazuleno, clorhidrato,

trans-8-cloro-5-metil-1-(4-fenoxi-ciclohexil)-5,6-dihidro-4H-2,3,5,10b-
tetraaza-benzo[e]azuleno,

trans-1-[8-cloro-1-(4-fenoxi-ciclohexil)-4H,6H-2,3,5,10b-tetraaza-
benzoazulen-5-il]-etanona,

trans-8-cloro-5-metanosulfonil-1-(4-fenoxi-ciclohexil)-5,6-dihidro-4H-
2,3,5,10b-tetraaza-benzoazuleno,

trans-2-[8-cloro-1-(4-fenoxi-ciclohexil)-4H,6H-2,3,5,10b-tetraaza-
benzoazulen-5-il]-etanol,

trans-8-cloro-5-isopropil-1-(4-fenoxi-ciclohexil)-5,6-dihidro-4H-2,3,5,10b-
tetraaza-benzoazuleno,

dimetilamida del ácido trans-8-cloro-1-(4-fenoxi-ciclohexil)-4H,6H-2,3,5,10b-
tetraaza-benzoazuleno-5-sulfónico,

trans-8-cloro-1-(4-fenoxi-ciclohexil)-5-piridin-2-ilmetil-5,6-dihidro-4H-
2,3,5,10b-tetraaza-benzoazuleno,

trans-1-[8-cloro-1-(4-fenoxi-ciclohexil)-4H,6H-2,3,5,10b-tetraaza-
benzoazulen-5-il]-2-dimetilamino-etanona,

trans-8-fluor-1-(4-fenoxi-ciclohexil)-4H,6H-2,3,5,10b-tetraaza-
benzo[e]azuleno-5-carboxilato de tert-butilo,

trans-8-fluor-5-metil-1-(4-fenoxi-ciclohexil)-5,6-dihidro-4H-2,3,5,10b-
tetraaza-benzoazuleno,

cis-8-cloro-1-(4-fenoxi-ciclohexil)-4H,6H-2,3,5,10b-tetraaza-benzoazuleno-5-carboxilato de tert-butilo,

cis-8-cloro-5-metil-1-(4-fenoxi-ciclohexil)-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazuleno,

trans-8-cloro-1-[4-(4-fluor-fenoxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzoazuleno-5-carboxilato de tert-butilo,

trans-8-cloro-1-[4-(4-fluor-fenoxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azuleno, clorhidrato,

trans-8-cloro-1-[4-(4-fluor-fenoxi)-ciclohexil]-5-metil-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazuleno,

trans-8-cloro-1-[4-(4-ciano-fenoxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azuleno-5-carboxilato de tert-butilo,

trans-4-[4-(8-cloro-5-metil-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-il)-ciclohexiloxi]-benzonitrilo,

trans-8-cloro-1-[4-(4-trifluormetil-fenoxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azuleno-5-carboxilato de tert-butilo,

trans-8-cloro-1-[4-(3-cloro-fenoxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzoazuleno-5-carboxilato de tert-butilo,

trans-8-cloro-1-[4-(3-cloro-fenoxi)-ciclohexil]-5-metil-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazuleno,

trans-8-cloro-1-[4-(3-metoxi-fenoxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzoazuleno-5-carboxilato de tert-butilo,

trans-8-cloro-1-[4-(3-metoxi-fenoxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azuleno, clorhidrato,

trans-8-cloro-1-[4-(3-metoxi-fenoxi)-ciclohexil]-5-metil-5,6-dihidro-4H-
2,3,5,10b-tetraaza-benzoazuleno,
trans-3-[4-(8-cloro-5-metil-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazulen-1-
il)-ciclohexiloxi]-benzonitrilo,
trans-8-cloro-1-(4-m-toliloxi-ciclohexil)-4H,6H-2,3,5,10b-tetraaza-
benzo[e]azuleno-5-carboxilato de tert-butilo,
trans-8-cloro-1-(4-m-toliloxi-ciclohexil)-5,6-dihidro-4H-2,3,5,10b-tetraaza-
benzo[e]azuleno, clorhidrato,
trans-8-cloro-5-metil-1-(4-m-toliloxi-ciclohexil)-5,6-dihidro-4H-2,3,5,10b-
tetraaza-benzo[e]azuleno,
trans-1-[4-(3-tert-butil-fenoxi)-ciclohexil]-8-cloro-4H,6H-2,3,5,10b-tetraaza-
benzo[e]azuleno-5-carboxilato de tert-butilo,
trans-8-cloro-1-[4-(2-fluor-fenoxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-
benzo[e]azuleno-5-carboxilato de tert-butilo,
trans-8-cloro-1-[4-(2-fluor-fenoxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-
tetraaza-benzo[e]azuleno, clorhidrato,
trans-8-cloro-1-[4-(2-fluor-fenoxi)-ciclohexil]-5-metil-5,6-dihidro-4H-
2,3,5,10b-tetraaza-benzo[e]azuleno,
trans-8-cloro-1-[4-(2-ciano-fenoxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-
benzoazuleno-5-carboxilato de tert-butilo,
trans-2-[4-(8-cloro-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-il)-
ciclohexiloxi]-benzonitrilo, clorhidrato,
trans-2-[4-(8-cloro-5-metil-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazulen-1-
il)-ciclohexiloxi]-benzonitrilo,

trans-8-cloro-1-(4-o-toliloxi-ciclohexil)-4H,6H-2,3,5,10b-tetraaza-benzoazuleno-5-carboxilato de tert-butilo,

trans-8-cloro-5-metil-1-(4-o-toliloxi-ciclohexil)-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazuleno,

trans-8-cloro-1-[4-(3,5-difluor-fenoxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzoazuleno-5-carboxilato de tert-butilo,

trans-8-cloro-1-[4-(3,5-difluor-fenoxi)-ciclohexil]-5-metil-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazuleno,

trans-8-cloro-1-[4-(naftalen-2-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzoazuleno-5-carboxilato de tert-butilo,

trans-8-cloro-5-metil-1-[4-(naftalen-2-iloxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazuleno,

trans-8-cloro-1-[4-(piridin-3-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzoazuleno-5-carboxilato de tert-butilo,

trans-8-cloro-5-metil-1-[4-(piridin-3-iloxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazuleno,

trans-8-cloro-1-[4-(5-cloro-piridin-3-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzoazuleno-5-carboxilato de tert-butilo,

trans-8-cloro-1-[4-(5-cloro-piridin-3-iloxi)-ciclohexil]-5-metil-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazuleno,

trans-8-cloro-1-[4-(piridin-2-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzoazuleno-5-carboxilato de tert-butilo,

trans-8-cloro-1-[4-(piridin-2-iloxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazuleno, clorhidrato,

trans-8-cloro-5-metil-1-[4-(piridin-2-iloxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzoazuleno,

trans-8-cloro-1-[4-(6-cloro-piridin-2-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azuleno-5-carboxilato de tert-butilo,

trans-8-cloro-1-[4-(6-cloro-piridin-2-iloxi)-ciclohexil]-5-metil-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azuleno,

trans-8-cloro-1-[4-(5-cloro-piridin-2-iloxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azuleno, clorhidrato,

trans-8-cloro-1-[4-(5-cloro-piridin-2-iloxi)-ciclohexil]-5-metil-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azuleno,

trans-8-cloro-1-[4-(pirimidin-2-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azuleno-5-carboxilato de tert-butilo,

cis-8-cloro-1-[4-(pirimidin-2-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azuleno-5-carboxilato de tert-butilo,

trans-8-cloro-5-metil-1-[4-(pirimidin-2-iloxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azuleno,

trans-8-cloro-1-[4-(pirazin-2-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azuleno-5-carboxilato de tert-butilo,

trans-8-cloro-5-metil-1-[4-(pirazin-2-iloxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azuleno,

trans-8-cloro-1-[4-(pirimidin-4-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azuleno-5-carboxilato de tert-butilo,

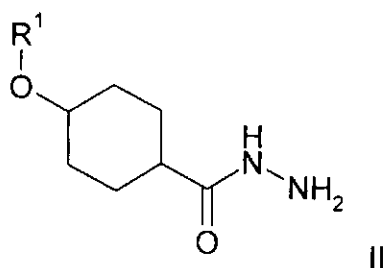
trans-8-cloro-5-metil-1-[4-(pirimidin-4-iloxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azuleno,

trans-8-cloro-1-[4-(piridazin-3-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azuleno-5-carboxilato de tert-butilo,

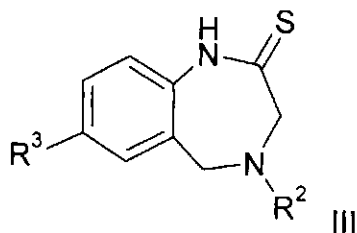
cis-8-cloro-1-[4-(piridazin-3-iloxi)-ciclohexil]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azuleno-5-carboxilato de tert-butilo,

trans-8-cloro-5-metil-1-[4-(piridazin-3-iloxi)-ciclohexil]-5,6-dihidro-4H-2,3,5,10b-tetraaza-benzo[e]azuleno,

6. Un proceso para la preparación del compuesto de la fórmula I según una cualquiera de las reivindicaciones de 1 a 5, que consiste en el paso de la reacción de un compuesto de la fórmula II



con un compuesto de la fórmula (III)



para obtener un compuesto de la fórmula (I), en la que R^1 , R^2 y R^3 tienen los significados definidos en la reivindicación 1.

7. Un compuesto de la fórmula I que se obtiene por el proceso según la reivindicación 6.

8. Un compuesto de la fórmula I según cualquiera de las reivindicaciones 1 a 5 para el uso en la prevención o el tratamiento de la dismenorrea, disfunción sexual masculina o femenina, hipertensión, fallo cardíaco crónico, secreción inapropiada de vasopresina, cirrosis hepática, síndrome nefrótico, ansiedad, trastornos depresivos, trastorno obsesivo-compulsivo, trastornos del espectro autista, esquizofrenia y comportamiento agresivo.

9. Una composición farmacéutica que contiene un compuesto de la fórmula I según una cualquiera de las reivindicaciones 1 a 5.

10. Una composición farmacéutica según la reivindicación 9, que es útil para la prevención o el tratamiento de la dismenorrea, disfunción sexual masculina o femenina, hipertensión, fallo cardíaco crónico, secreción inapropiada de vasopresina, cirrosis hepática, síndrome nefrótico, ansiedad, trastornos depresivos, trastorno obsesivo-compulsivo, trastornos del espectro autista, esquizofrenia y comportamiento agresivo.

11. Uso de un compuesto de la fórmula I según una cualquiera de las reivindicaciones 1 a 5 para la preparación de un medicamento.

12. Uso según la reivindicación 11, en el que el medicamento es útil para la prevención o el tratamiento de la dismenorrea, disfunción sexual masculina o femenina, hipertensión, fallo cardíaco crónico, secreción inapropiada de vasopresina, cirrosis hepática, síndrome nefrótico, ansiedad, trastornos depresivos, trastorno obsesivo-compulsivo, trastornos del espectro autista, esquizofrenia y comportamiento agresivo.

13. La invención según se describe anteriormente.

Traducido según mi mejor saber y entender, este día 5 de mayo de 2011, en la ciudad de Bogotá, D.C., por Anita Escobar de Tamayo, Traductora Oficial, Res. 2177 de 1989, Ministerio de Justicia, República de Colombia.

TRADUCTORA OFICIAL
RES. 2177/89 MINJUSTICIA


ANITA ESCOBAR DE TAMAYO

Bescheinigung

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

Certificate

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Attestation

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr.

Patent application No.

Demande de brevet n°

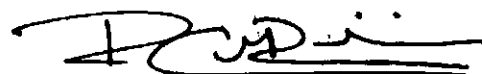
08170188.0 / EP08170188

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP08170188.

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.



R.C. van Dijk

Anmeldung Nr:
Application no.: 08170188.0
Demande no.:

Anmeldetag:
Date of filing: 28.11.08
Date de dépôt:

Anmelder / Applicant(s) / Demandeur(s):

F. Hoffmann-La Roche AG
Grenzacherstrasse 124
4070 Basel/CH

Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Arylcyclohexylethers of Dihydrotetraazabenzazulenes

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

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biological aspects of the vasopressin type-2 receptor and aquaporin 2 water channel in nephrogenic diabetes insipidus"). Compounds with activity at the V2 receptor may 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 behaviours in both females and males"). Central oxytocin receptor antagonism might therefore lead to anxiogenic effects, which are regarded as undesired side-effects

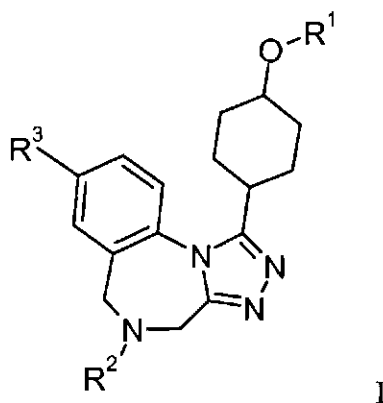
In the brain vasopressin acts as a neuromodulator and is elevated in the amygdala during stress (Ebner, et al. (2002). *Eur J Neurosci.* **15**, 384-8., "Forced swimming triggers vasopressin release within the amygdala to modulate stress-coping strategies in rats"). It is known that stressful life events 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 V1a 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 V1a 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 V1a receptor knockout mice"). The downregulation of the V1a receptor using antisense oligonucleotide injection in the septum also causes a reduction in anxious behavior (Landgraf, et al. (1995). *Regul Pept.* **59**, 229-39., "V1 vasopressin receptor antisense oligodeoxynucleotide into septum reduces vasopressin binding, social discrimination abilities, and anxiety-related behavior in rats"). Vasopressin or the V1a receptor are also implicated in other neuropsychological disorders: genetic studies recently linked sequence polymorphism in the promoter of the human V1a receptor to autistic spectrum disorders (Yirmiya, et al. (2006). **11**, 488-94, "Association between the arginine vasopressin 1a receptor (AVPR1a) gene and autism in a family-based study: mediation by socialization skills"), intranasal administration of vasopressin was shown to influence aggression in human males (Thompson, et al. (2004). *Psychoneuroendocrinology.* **29**, 35-48, "The effects of vasopressin on

Case 25355

Arylcyclohexylethers of Dihydrotetraazabenzazulenes

The present invention is concerned with arylcyclohexylethers of dihydro-tetraazabenzazulene derivatives, i.e. arylcyclohexylethers of 5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene derivatives, which act as V1a receptor modulators, and in particular as V1a receptor antagonists, their manufacture, pharmaceutical compositions containing them and their
5 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.

10 In particular, the present invention is concerned with arylcyclohexylethers of dihydro-tetraazabenzazulene derivatives of formula I



wherein R¹, R² and R³ are as described in claim 1.

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

Three vasopressin receptors, all belonging to the class I G-protein coupled receptors, are known. The V1a receptor is expressed in the brain, liver, vascular smooth muscle, lung, uterus and testis, the V1b or V3 receptor is expressed in the brain and pituitary gland, the V2 receptor is
20 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

human facial responses related to social communication") and vasopressin levels were found to be elevated in schizophrenic patients (Raskind, et al. (1987). *Biol Psychiatry*. **22**, 453-62, "Antipsychotic drugs and plasma vasopressin in normals and acute schizophrenic patients") and patients with obsessive-compulsive disorder (Altemus, et al. (1992). *Arch Gen Psychiatry*. **49**, 9-20, "Abnormalities in the regulation of vasopressin and corticotropin releasing factor secretion in obsessive-compulsive disorder").

The V1a 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 V1a 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, V1a antagonists with improved penetration through the blood-brain barrier are expected to be of advantage.

A vasopressin V1a 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 V1a vasopressin receptor antagonist, in the prevention of dysmenorrhoea"). V1a 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 V1a 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").

It is an object of the present invention to provide compounds which act as V1a receptor modulators, and in particular as V1a receptor antagonists. It is a further object of the invention to provide selective inhibitors of the V1a receptor since it is expected that selectivity affords a low potential to cause unwanted off-target related side effects such as discussed above.

Such V1a 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. The preferred 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 V1a activity may 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 term "alkyl" denotes a saturated, i.e. aliphatic hydrocarbon group including a straight or branched carbon chain. If not further specified, "alkyl" groups denote groups with 1 to 12 carbon atoms. Examples for "alkyl" are methyl, ethyl, propyl, isopropyl, n-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl and the like.

The term "alkoxy" denotes a group -O-R' wherein R' is alkyl as defined above.

The term "aromatic" means the presence of an electron sextet in a ring, according to Hückel's rule.

The term "aryl" denotes a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono- or bicyclic aromatic ring. Preferred aryl are phenyl or naphthyl. Aryl may be unsubstituted or substituted as described herein.

The term "cyano" denotes the group -CN.

The term "halo" or "halogen" denotes chloro, iodo, fluoro and bromo.

The term "halo-C_{1-n}-alkyl" or "C_{1-n}-haloalkyl" denotes a C_{1-n}-alkyl group as defined above, with 1 to n carbon atoms, wherein at least one of the hydrogen atoms of the alkyl group is replaced by a halogen atom, preferably fluoro or chloro, most preferably fluoro. Examples of halo-C_{1-n}-alkyl include but are not limited to methyl, ethyl, propyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl or n-hexyl substituted by one or more Cl, F, Br or I atom(s), in particular one, two or three fluoro or chloro, as well as those groups specifically illustrated by the examples herein below. Among the preferred halo-C_{1-n}-alkyl groups are difluoro- or trifluoro-methyl or -ethyl.

The term "hydroxy-C_{1-n}-alkyl" or "C_{1-n}-hydroxyalkyl" denotes a C_{1-n}-alkyl group as defined above, with 1 to n carbon atoms, wherein at least one of the hydrogen atoms of the alkyl

group is replaced by a hydroxy, i.e. by an OH group. An example for hydroxyalkyl is hydroxyethyl.

5 The term "heteroaryl" refers to a monovalent 5- or 6-membered aromatic monocyclic or 9- or 10-membered aromatic bicyclic ring containing from one to four ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. Preferably, the monocyclic heteroaryl bears one or two heteroatoms and the bicyclic heteroaryl bears from one to four heteroatoms. 6-Membered heteroaryl are preferred. Examples for heteroaryl moieties include but are not limited to pyridinyl, pyrimidinyl, pyridazinyl or pyrazinyl. Heteroaryl may be unsubstituted or substituted as described herein.

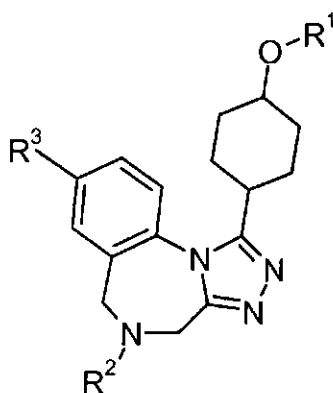
10 The term "heterocycloalkyl" as defined herein refers to a monovalent 3 to 7 membered saturated ring containing one or two heteroatoms selected from N, O or S. Examples for heterocycloalkyl moieties are tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl. Heterocycloalkyl is optionally substituted as described herein.

15 The term "oxo" when referring to substituents on heterocycloalkyl means that an oxygen atom is attached to the heterocycloalkyl ring. Thereby, the "oxo" may either replace two hydrogen atoms on a carbon atom, or it may simply be attached to sulfur, so that the sulfur exists in oxidized form, i.e. bearing one or two oxygens.

20 When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents. Thereby, one, two or three substituents are preferred. Even more preferred are one or two substituents or one substituent.

25 The term "pharmaceutically acceptable salt" or "pharmaceutically acceptable acid addition salt" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

In detail, the present invention relates to compounds of the general formula (I)



I

Rⁱ is aryl or heteroaryl, unsubstituted or substituted with one or more substituents independently selected from A;

5 Rⁱⁱ is H,

C₁₋₁₂-alkyl, unsubstituted or substituted with one or more OH, halo, cyano or C₁₋₁₂-alkoxy, -(CH₂)_q-R^a, wherein R^a is phenyl or 5- or 6-membered heteroaryl, each unsubstituted or substituted with one or more substituents independently selected from A,

-(CH₂)_rNRⁱRⁱⁱ,

10 -C(O)-C₁₋₁₂-alkyl, wherein C₁₋₁₂-alkyl is unsubstituted or substituted with one or more OH, halo, cyano or C₁₋₁₂-alkoxy,

-C(O)(CH₂)_qOC(O)-C₁₋₁₂-alkyl,

-C(O)(CH₂)_qNRⁱRⁱⁱ,

15 -C(O)O-C₁₋₁₂-alkyl, wherein alkyl is unsubstituted or substituted with one or more OH, halo, cyano or C₁₋₁₂-alkoxy,

-S(O)₂-C₁₋₁₂-alkyl,

-S(O)₂NRⁱRⁱⁱ,

Rⁱ and Rⁱⁱ are each independently H, C₁₋₁₂-alkyl, or form together with the nitrogen to which they are bound a 3- to 7-membered heterocycloalkyl containing one or two heteroatoms selected from N, O or S, which heterocycloalkyl is unsubstituted or substituted by one or more substituents independently selected from B,

q is 1, 2, 3 or 4,

r is 2, 3 or 4,

A is halo, cyano, OH, C₁₋₇-alkyl, halo-C₁₋₇-alkyl, C₁₋₇-alkoxy, halo-C₁₋₇-alkoxy, or 25 hydroxy-C₁₋₇-alkyl,

B is oxo, halo, OH, C₁₋₇-alkyl or C₁₋₇-alkoxy,

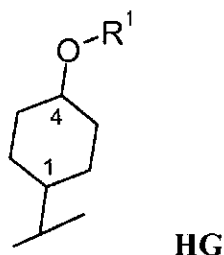
R³ is Cl or F,

or a pharmaceutically acceptable salt thereof.

The compounds of formula I may contain asymmetric carbon atoms. Accordingly, the 30 present invention includes all stereoisomeric forms of the compounds of formula I, including

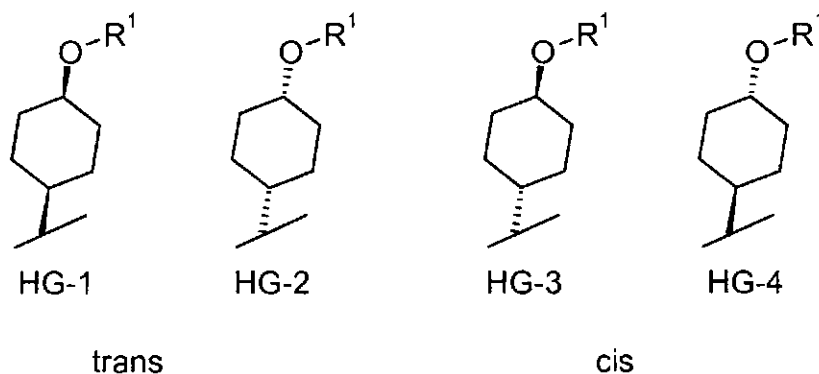
each of the individual stereoisomer and mixtures thereof, i.e. their individual optical isomers and mixtures thereof.

This applies in particular to the alkylcyclohexylether-head group (HG) of the compounds of formula 1, namely



wherein at least the carbon atoms 1 and 4 are asymmetric carbon atoms and R¹ could further comprise asymmetric carbon atoms. It is to be understood that present invention includes all individual stereoisomers of head groups and mixtures thereof.

10 In particular, these head groups HG are:



It is further understood that all embodiments of the invention as described herein may be combined with each other.

In certain embodiments,

15 A is halo, cyano, OH, C₁₋₇-alkyl, halo-C₁₋₇-alkyl, C₁₋₇-alkoxy, halo-C₁₋₇-alkoxy, or hydroxy-C₁₋₇-alkyl.

In certain embodiments, A is halo, cyano, C₁₋₇-alkyl, halo-C₁₋₇-alkyl, or C₁₋₇-alkoxy.

In certain embodiments, R¹ is

aryl or heteroaryl, unsubstituted or substituted with one or more substituents

20 independently selected from A; and A is as defined above.

In certain embodiments, R¹ is

a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono- or bicyclic aromatic ring,

a monovalent 5- or 6-membered aromatic monocyclic or 9- or 10-membered aromatic

bicyclic ring containing from one to four ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, each unsubstituted or substituted with one or more substituents independently selected from A; and A is as defined above.

5 In certain embodiments, R^1 is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl or pyrazinyl, each unsubstituted or substituted with one or more substituents independently selected from A; and A is as defined above.

In certain embodiments, R^1 is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl or pyrazinyl, each unsubstituted or substituted with one or more substituents independently selected
10 from methyl, t-butyl, Cl, F, trifluoromethyl, methoxy or cyano.

In certain embodiments, R^1 is phenyl, 4-fluoro-phenyl, 4-cyanophenyl, 4-trifluoromethyl-phenyl, 3-chloro-phenyl, 3-methoxy-phenyl, 3-cyano-phenyl, 3-methyl-phenyl, 3-t-butyl-phenyl, 3-trifluoromethyl-phenyl, 2-fluoro-phenyl, 2-cyano-phenyl, 2-methyl-phenyl, 3,5-di-fluoro-phenyl, naphth-2-yl, naphth-1-yl, pyridin-3-yl, 5-chloro-pyridin-3-yl, pyridin-2-yl, 6-chloro-
15 pyridin-2-yl, 2,6-di-methyl-pyrimidin-4-yl, pyrimidin-2-yl, pyrazin-2-yl, pyridin-4-yl or pyridazin-3-yl.

In certain embodiments, R^2 is as described above.

In certain embodiments, R^2 is H. Thereby, forming either the free base or a pharmaceutically acceptable acid addition salt with an inorganic or organic acid such as
20 hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

In certain embodiments, R^2 is C_{1-12} -alkyl, unsubstituted or substituted with one or more OH, halo, cyano or C_{1-12} -alkoxy. In certain embodiments, R^2 is C_{1-12} -alkyl, unsubstituted or
25 substituted with one or more OH.

In certain embodiments, R^2 is $-(CH_2)_q-R^a$, wherein R^a is phenyl or 5- or 6-membered heteroaryl, each unsubstituted or substituted with one or more substituents independently selected from A, and A is as defined above and q is 1, 2, 3 or 4, preferably 1. In certain
30 embodiments, R^2 is $-(CH_2)_q-R^a$, wherein R^a is phenyl or 5- or 6-membered heteroaryl, each unsubstituted or substituted with one or more substituents independently selected from A, and A is halo, cyano, OH, C_{1-7} -alkyl, halo- C_{1-7} -alkyl, or C_{1-7} -alkoxy; and q is 1, 2, 3 or 4, preferably 1. In certain embodiments, R^2 is $-(CH_2)_q-R^a$, wherein R^a is phenyl or 5- or 6-membered heteroaryl

and q is 1, 2, 3 or 4, preferably 1. In certain embodiments, R^2 is $-\text{CH}_2\text{-pyridinyl}$ or benzyl , preferably $-\text{CH}_2\text{-pyridin-2-yl}$.

In certain embodiments, R^2 is $-\text{C(O)-C}_{1-12}\text{-alkyl}$, wherein alkyl is unsubstituted or substituted with one or more OH, halo, cyano or $\text{C}_{1-12}\text{-alkoxy}$. In certain embodiments, R^2 is -
5 $\text{C(O)-C}_{1-12}\text{-alkyl}$.

In certain embodiments, R^2 is $-\text{C(O)(CH}_2)_q\text{NR}^i\text{R}^{ii}$, wherein q is 1, 2, 3 or 4, preferably 1, and wherein wherein R^i and R^{ii} are each independently H, $\text{C}_{1-12}\text{-alkyl}$, or form together with the nitrogen to which they are bound a 3- to 7-membered heterocycloalkyl containing one or two heteroatoms selected from N, O or S, which heterocycloalkyl is unsubstituted or substituted by
10 one or more substituents independently selected from B, and B is oxo, halo, OH, $\text{C}_{1-7}\text{-alkyl}$ or $\text{C}_{1-7}\text{-alkoxy}$. In certain embodiments, R^2 is $\text{C(O)(CH}_2)_q\text{NR}^i\text{R}^{ii}$, wherein q is 1, 2, 3 or 4, preferably 1, and wherein R^i and R^{ii} are each independently H or $\text{C}_{1-12}\text{-alkyl}$, preferably $\text{C}_{1-12}\text{-alkyl}$.

In certain embodiments, R^2 is $-\text{C(O)O-C}_{1-12}\text{-alkyl}$, wherein alkyl is unsubstituted or substituted with one or more OH, halo, cyano or $\text{C}_{1-12}\text{-alkoxy}$. In certain embodiments, R^2 is
15 $-\text{C(O)O-C}_{1-12}\text{-alkyl}$.

In certain embodiments, R^2 is $-\text{S(O)}_2\text{-C}_{1-12}\text{-alkyl}$.

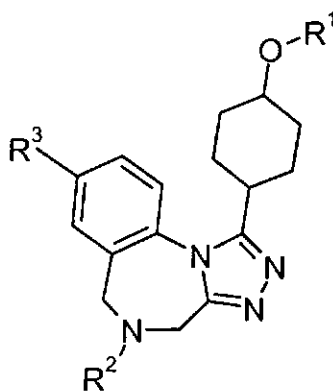
In certain embodiments, R^2 is $-\text{S(O)}_2\text{NR}^i\text{R}^{ii}$, wherein R^i and R^{ii} are each independently H, $\text{C}_{1-12}\text{-alkyl}$, or form together with the nitrogen to which they are bound a 3- to 7-membered heterocycloalkyl containing one or two heteroatoms selected from N, O or S, which
20 heterocycloalkyl is unsubstituted or substituted by one or more substituents independently selected from B, and B is oxo, halo, OH, $\text{C}_{1-7}\text{-alkyl}$ or $\text{C}_{1-7}\text{-alkoxy}$. In certain embodiments, R^2 is $-\text{S(O)}_2\text{NR}^i\text{R}^{ii}$, wherein R^i and R^{ii} are each independently H or $\text{C}_{1-12}\text{-alkyl}$, preferably $\text{C}_{1-12}\text{-alkyl}$.

In certain embodiments,
 R^2 is H,
25 $\text{C}_{1-12}\text{-alkyl}$, unsubstituted or substituted with one or more OH,
 $-(\text{CH}_2)_q\text{-R}^a$, wherein R^a is phenyl or 5- or 6-membered heteroaryl and q is 1, 2, 3 or 4,
preferably 1,
 $-\text{C(O)-C}_{1-12}\text{-alkyl}$,
 $-\text{C(O)(CH}_2)_q\text{NR}^i\text{R}^{ii}$, wherein R^i and R^{ii} are each independently H or $\text{C}_{1-12}\text{-alkyl}$, preferably
30 $\text{C}_{1-12}\text{-alkyl}$, and q is 1, 2, 3 or 4, preferably 1,
 $-\text{C(O)O-C}_{1-12}\text{-alkyl}$,
 $-\text{S(O)}_2\text{-C}_{1-12}\text{-alkyl}$, or
 $-\text{S(O)}_2\text{NR}^i\text{R}^{ii}$, wherein R^i and R^{ii} are each independently H or $\text{C}_{1-12}\text{-alkyl}$, preferably
 $\text{C}_{1-12}\text{-alkyl}$.

In certain embodiments, R^2 is $-C(O)CH_2N(Me)_2$, $-C(O)Me$, $-CH_2$ -pyridin-2-yl, $-COO$ -t-butyl, $-S(O)_2Me$, $-S(O)_2N(Me)_2$, 2-hydroxy-ethyl, H, i-propyl or methyl.

In certain embodiment, R^3 is Cl or F. In certain embodiment, R^3 is Cl.

In a certain embodiment of the invention, the compound of formula I is provided



I

wherein

R^1 is a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono- or bicyclic aromatic ring,

a monovalent 5- or 6-membered aromatic monocyclic or 9- or 10-membered aromatic

bicyclic ring containing from one to four ring heteroatoms selected from N, O, or S, the remaining ring atoms being C,

each unsubstituted or substituted with one or more substituents independently selected from A;

R^2 is H,

C_{1-12} -alkyl, unsubstituted or substituted with one or more OH,

$-(CH_2)_q-R^a$, wherein R^a is phenyl or 5- or 6-membered heteroaryl and q is 1, 2, 3 or 4, preferably 1,

$-C(O)-C_{1-12}$ -alkyl,

$-C(O)(CH_2)_qNR^iR^{ii}$, wherein R^i and R^{ii} are each independently H or C_{1-12} -alkyl, preferably

C_{1-12} -alkyl, and q is 1, 2, 3 or 4, preferably 1,

$-C(O)O-C_{1-12}$ -alkyl,

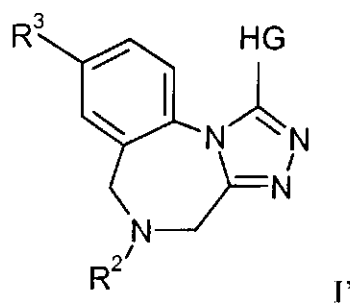
$-S(O)_2-C_{1-12}$ -alkyl, or

$-S(O)_2NR^iR^{ii}$, wherein R^i and R^{ii} are each independently H or C_{1-12} -alkyl, preferably C_{1-12} -alkyl,

R^3 is Cl or F,

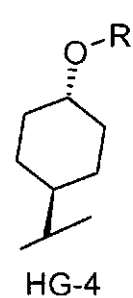
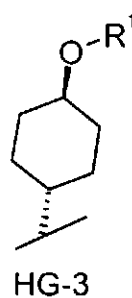
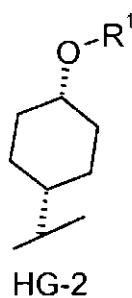
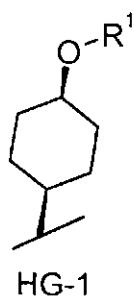
A is halo, cyano, OH, C_{1-7} -alkyl, halo- C_{1-7} -alkyl, or C_{1-7} -alkoxy, or a pharmaceutically acceptable salt thereof.

In a certain embodiment of the invention, the compound of formula I is provided as a subset of formula I'



wherein

5 HG is selected from



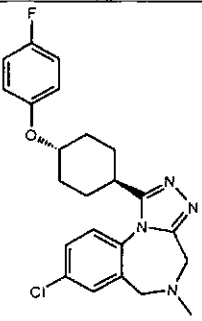
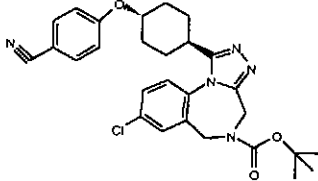
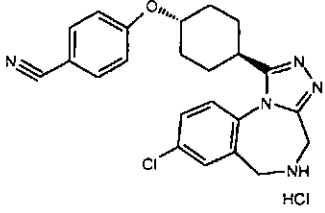
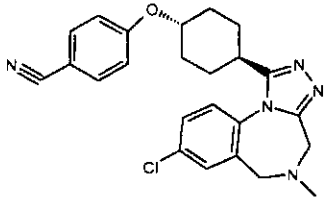
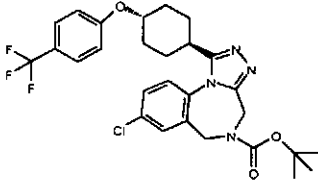
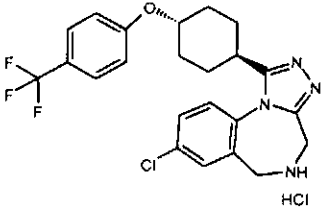
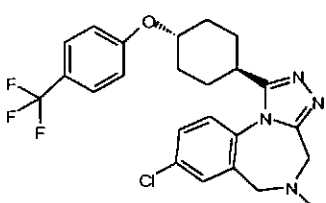
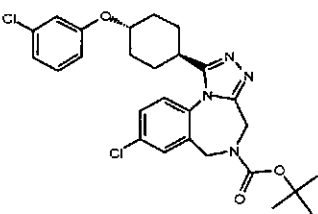
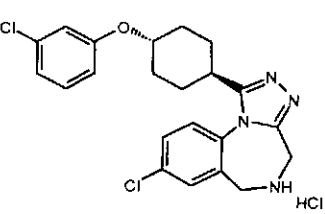
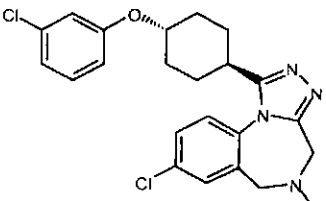
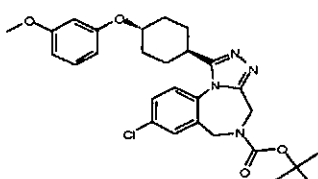
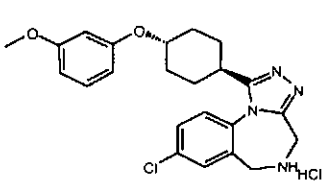
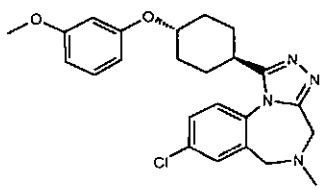
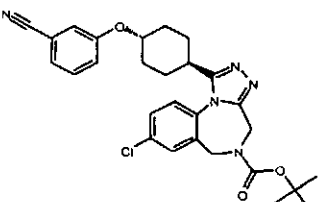
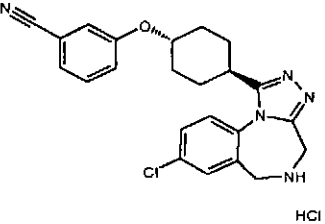
and R¹, R² and R³ are as described above, including all combinations thereof.

Examples for the compound according to the invention are shown in the experimental part:

Table 1:

Ex	Structure	Ex	Structure	Ex	Structure
1		2		3	

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46		47		48	

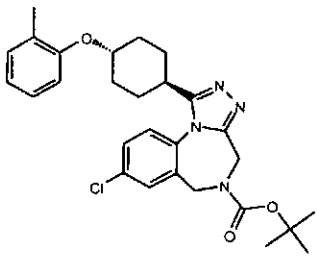
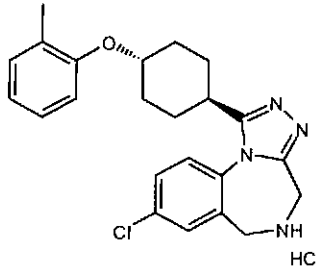
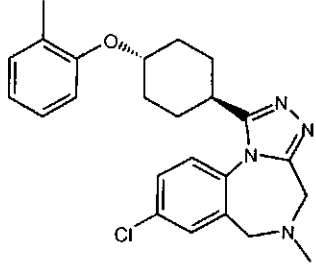
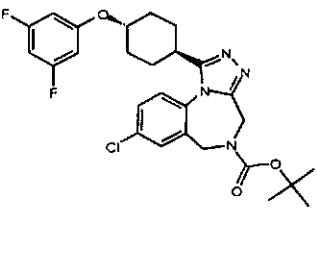
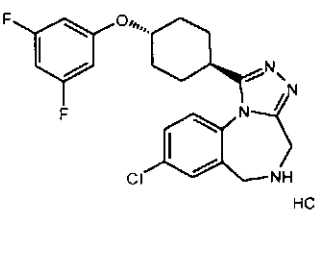
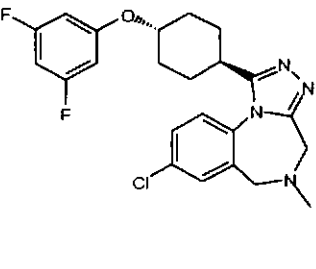
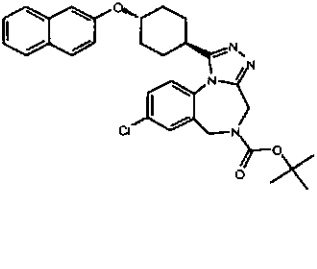
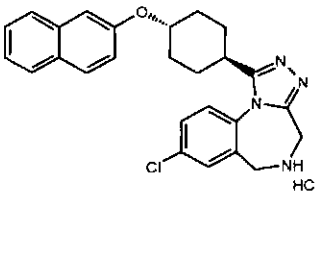
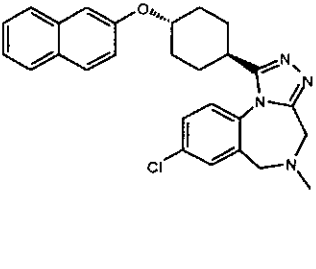
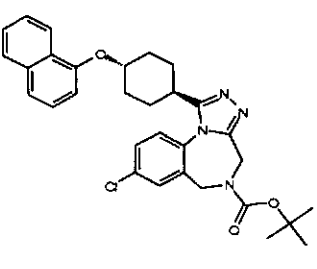
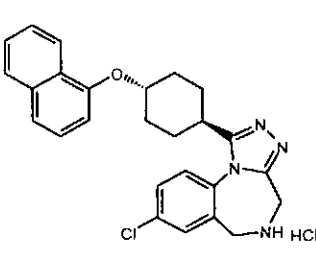
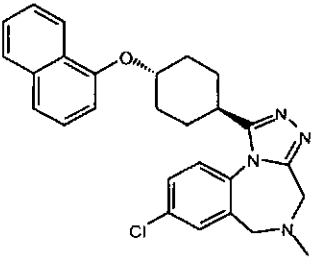
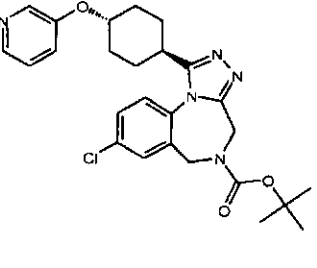
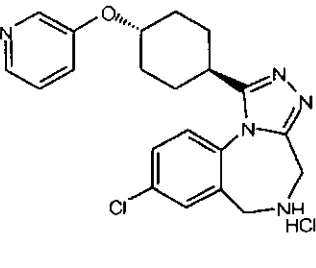
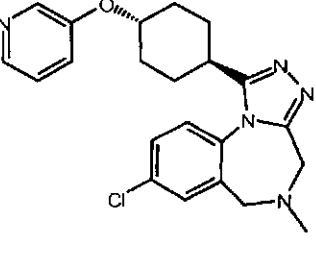
HCl

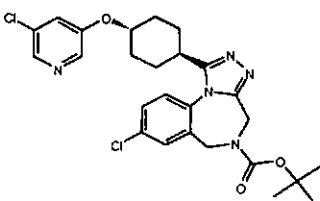
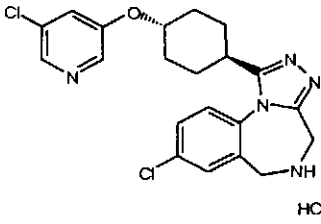
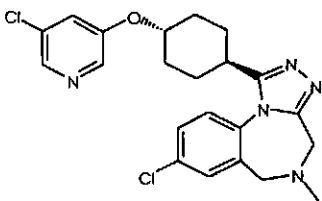
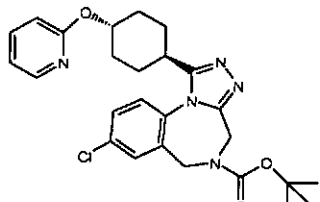
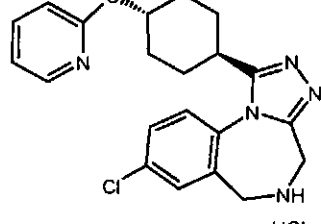
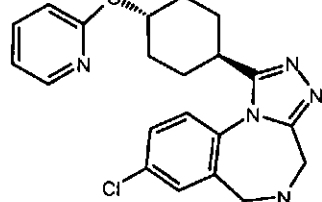
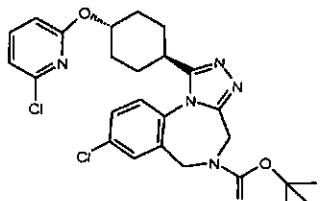
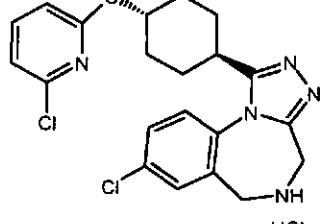
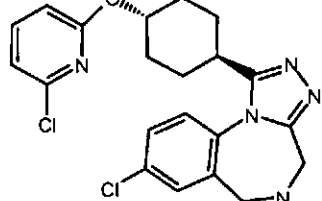
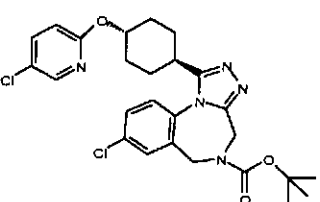
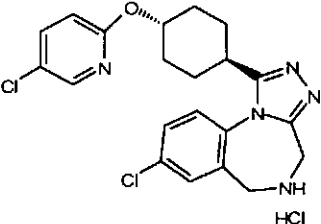
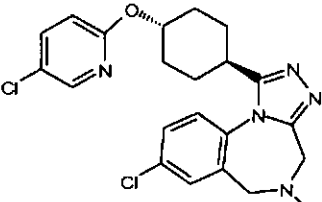
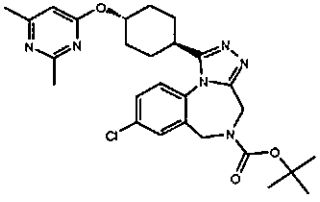
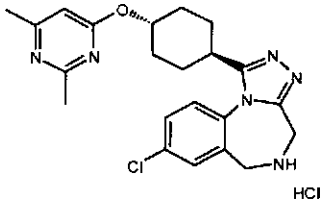
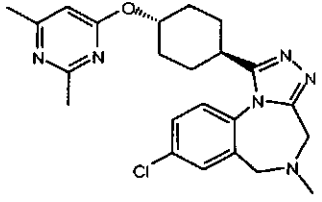
HCl

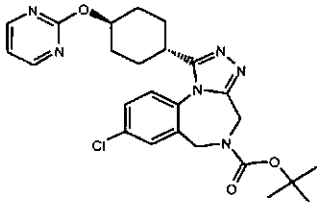
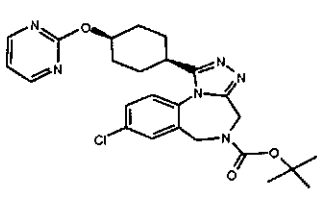
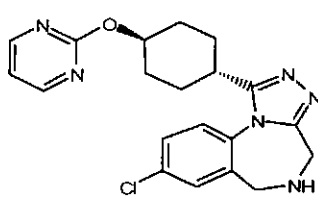
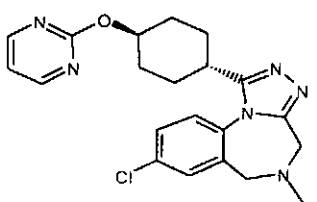
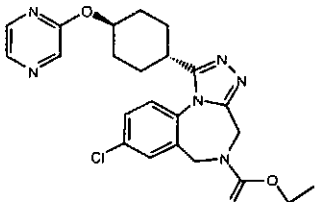
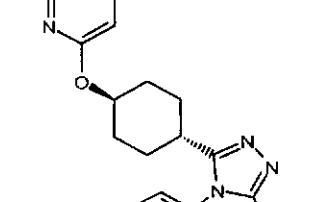
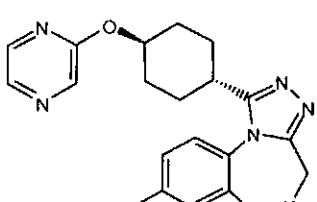
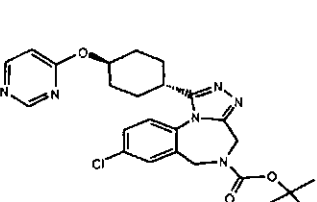
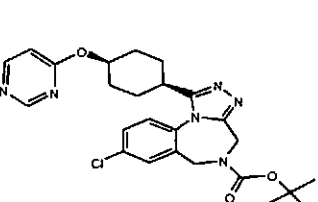
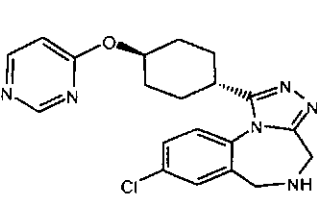
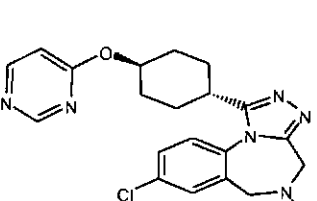
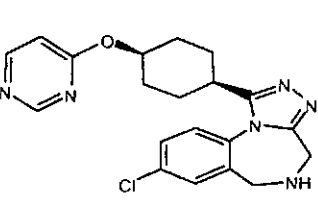
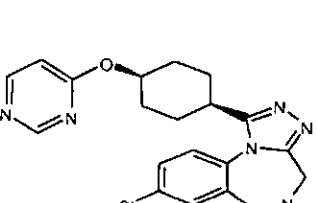
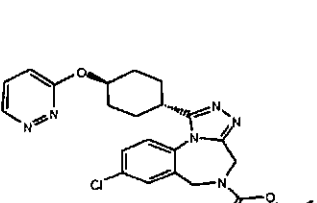
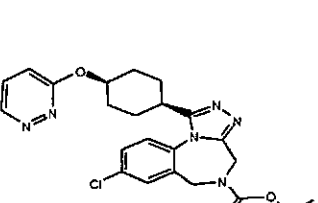
HCl

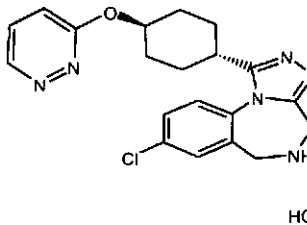
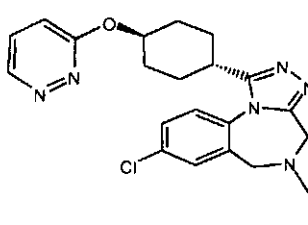
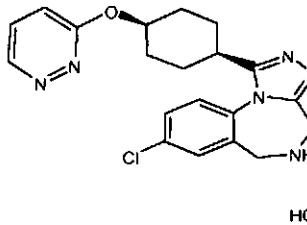
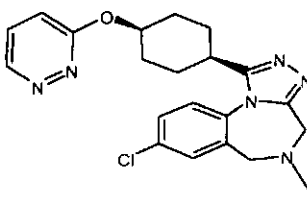
HCl

HCl

49		50		51	
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85		86		87	
88	 HCl	89		90	 HCl
91		92		93	

94	 HCl	95		96	 HCl
97					

Preferred compounds of the invention are shown in the examples.

Particularly preferred are

- trans-8-Chloro-1-(4-phenoxycyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-1-(4-phenoxycyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride,
- trans-8-Chloro-5-methyl-1-(4-phenoxycyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
- trans-1-[8-Chloro-1-(4-phenoxycyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-ethanone,
- trans-8-Chloro-5-methanesulfonyl-1-(4-phenoxycyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- trans-2-[8-Chloro-1-(4-phenoxycyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-ethanol,
- trans-8-Chloro-5-isopropyl-1-(4-phenoxycyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- trans-8-Chloro-1-(4-phenoxycyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-sulfonic acid dimethylamide,
- trans-8-Chloro-1-(4-phenoxycyclohexyl)-5-pyridin-2-ylmethyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,

- trans-1-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-
2-dimethylamino-ethanone,
- trans-8-Fluoro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-
carboxylic acid tert-butyl ester,
- 5 trans-8-Fluoro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzoazulene,
- cis-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-
carboxylic acid tert-butyl ester,
- cis-8-Chloro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
10 benzoazulene,
- trans-8-Chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzo[e]azulene hydrochloride,
- 15 trans-8-Chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-
tetraaza-benzoazulene,
- trans-8-Chloro-1-[4-(4-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid tert-butyl ester,
- trans-4-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-
20 cyclohexyloxy]-benzonitrile,
- trans-8-Chloro-1-[4-(4-trifluoromethyl-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,
- 25 trans-8-Chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-
tetraaza-benzoazulene,
- trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-
30 benzo[e]azulene hydrochloride,
- trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-
2,3,5,10b-tetraaza-benzoazulene,
- trans-3-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulen-1-yl)-
cyclohexyloxy]-benzonitrile,
- 35 trans-8-Chloro-1-(4-m-tolyloxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-
carboxylic acid tert-butyl ester,
- trans-8-Chloro-1-(4-m-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzo[e]azulene hydrochloride,

- trans-8-Chloro-5-methyl-1-(4-m-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzo[e]azulene,
trans-1-[4-(3-tert-Butyl-phenoxy)-cyclohexyl]-8-chloro-4H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid tert-butyl ester,
5 trans-8-Chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzo[e]azulene hydrochloride,
trans-8-Chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-
10 tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(2-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,
trans-2-[4-(8-Chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-
cyclohexyloxy]-benzonitrile hydrochloride,
15 trans-2-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulen-1-yl)-
cyclohexyloxy]-benzonitrile,
trans-8-Chloro-1-(4-o-tolyloxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-
carboxylic acid tert-butyl ester,
trans-8-Chloro-5-methyl-1-(4-o-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
20 benzoazulene,
trans-8-Chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-
2,3,5,10b-tetraaza-benzoazulene,
25 trans-8-Chloro-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-5-methyl-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-
2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(pyridin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
30 benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-5-methyl-1-[4-(pyridin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-
tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,
35 trans-8-Chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-
2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,

trans-8-Chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride,

trans-8-Chloro-5-methyl-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,

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

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

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

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

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

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

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

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

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

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

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

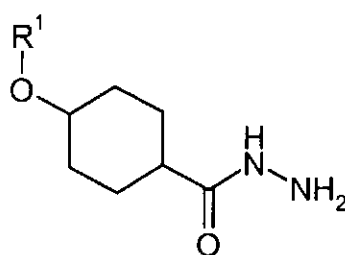
trans-8-Chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,

30 cis-8-Chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester, or

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

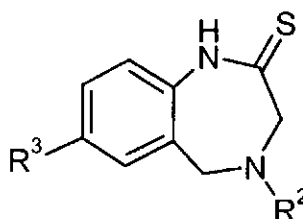
In a certain embodiment, the compounds of formula (I) of the invention can be

35 manufactured according to a process comprising the step of reacting a compound of formula (II):



II

with a compound of formula (III):

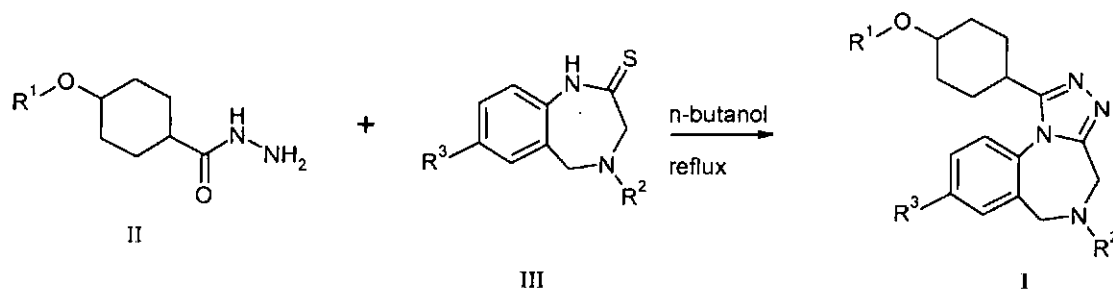


III

to obtain a compound of formula (I) wherein R¹, R² and R³ are as defined hereinabove for
5 formula (I).

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

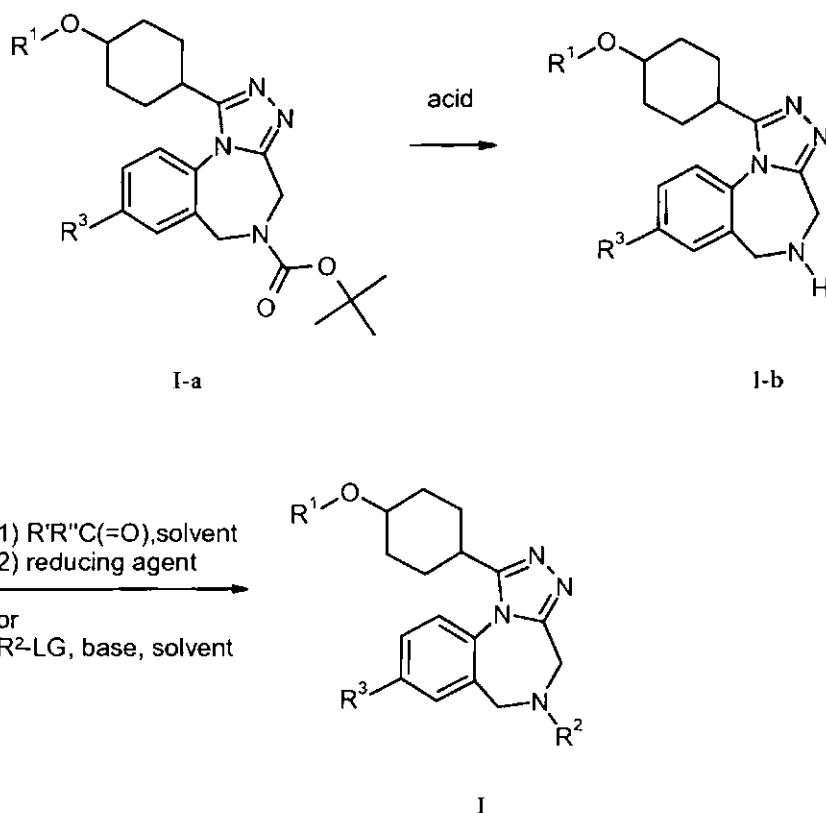
General scheme A



10 General scheme A

Compounds of formula (I) can be prepared by thermal condensation of a hydrazide derivative of
formula (II) and a thiolactam derivative 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 general scheme C as described hereinafter. General scheme A is hereinafter further
15 illustrated with general procedure V.

General scheme B

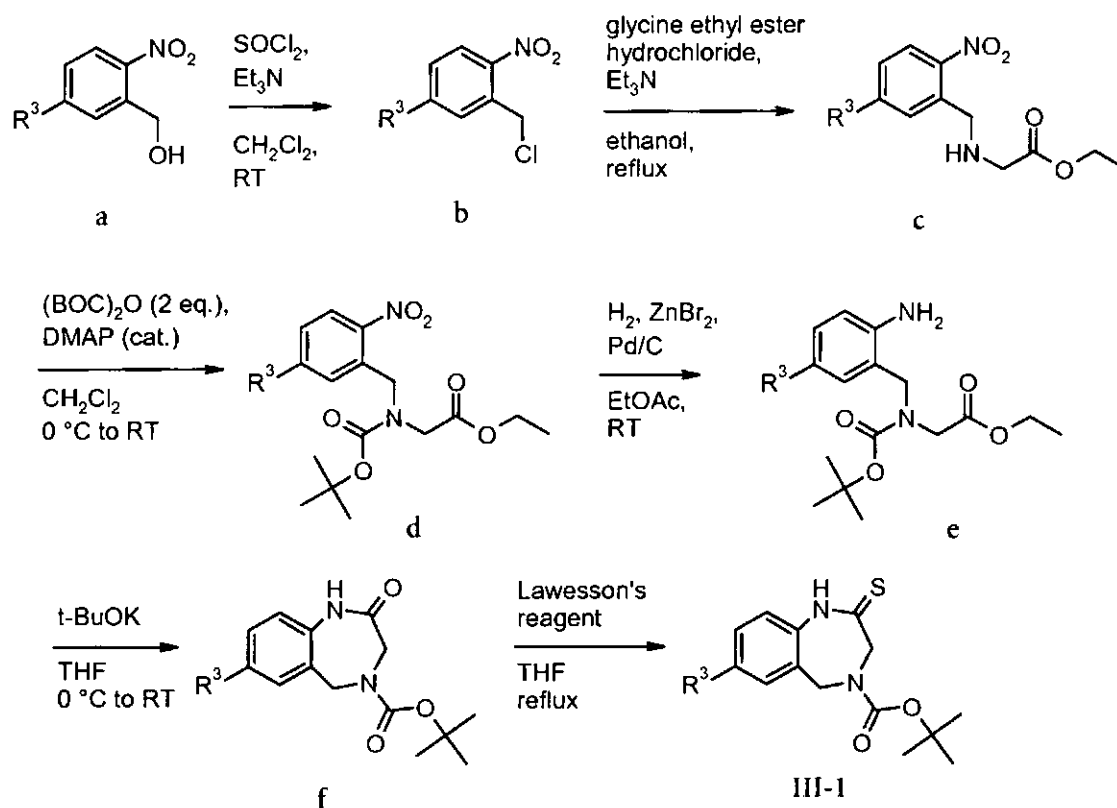


General scheme B

- Compounds of formula (I) with R² different from H can be prepared from compounds of formula (I-b) (compounds of formula (I) wherein R² is H) according to methods known in the art, e.g. by
- 5 treating a compound of formula (I-b) with an inorganic base such as a carbonate salt or an organic base such as a tertiary amine and an electrophilic reactant R²-LG (wherein LG is a leaving group, e.g. 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
 - 10 compound of formula (I-b) with a ketone or aldehyde and a suitable reducing agent, e.g. a borohydride derivative such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. Compounds of formula (I-b) can be obtained by cleavage of the substituent R² of compound of formula I using methods known in the art. Compounds of formula (I-b) are conveniently obtained as the salt or the free base after basic aqueous work-up by
 - 15 treatment of compounds of formula (I-a) (compounds of formula (I) in which R² is tert-butoxycarbonyl) with an acid in a suitable solvent, e.g. methanesulfonic acid in dichloromethane

or tetrahydrofuran or hydrochloric acid in methanol. General scheme C is hereinafter further illustrated with general procedures VI and VII.

General scheme C

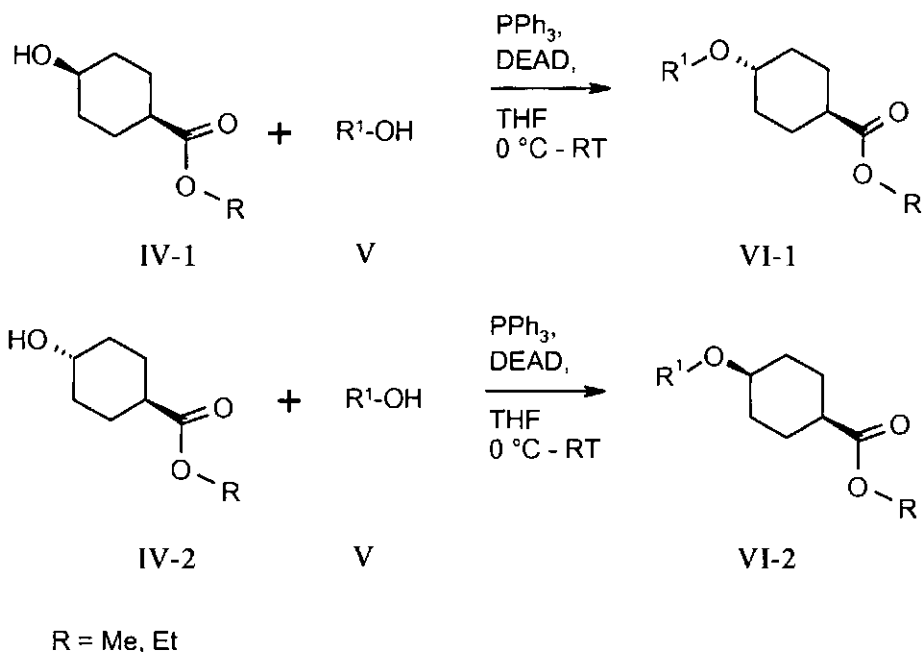


5 General scheme C

Thiolactam derivatives of formula (III-1) (compounds of formula (III) in which R^2 is tert-butoxycarbonyl) can be obtained as follows: Transformation of a 2-nitrobenzyl alcohol of formula (a) to a benzylic chloride of formula (b) can be effected 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 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 derivative of formula (III-1) is obtained by treatment of a compound of formula (f) with Lawesson's reagent

(2,4-bis-(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide) or phosphorous pentasulfide at elevated temperature.

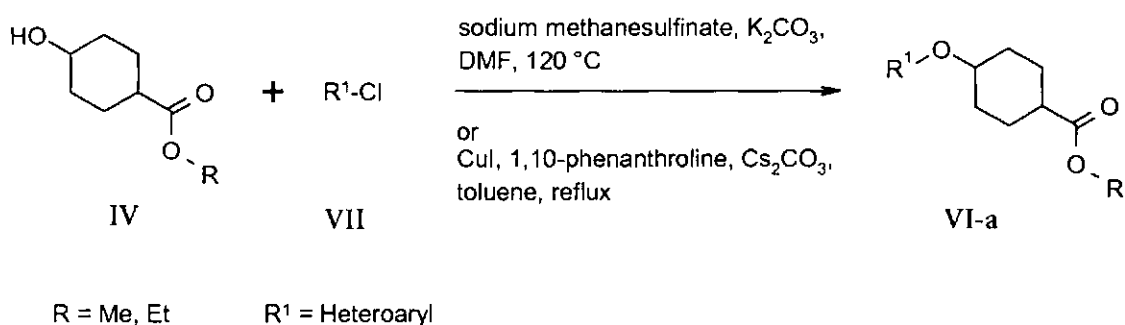
General scheme D



5 General scheme D

Etherification of a 4-hydroxy-cyclohexanecarboxylic acid ester of formula (IV) with a phenol derivative of formula (V) under Mitsunobu conditions leads to a 4-aryloxy-cyclohexanecarboxylic acid ester of formula (VI) under inversion of configuration. Thus trans-4-aryloxy-cyclohexanecarboxylic acid esters of formula (VI-1) are obtained from a cis-4-hydroxy-cyclohexanecarboxylic acid ester of formula (IV-1), while cis-4-aryloxy-cyclohexanecarboxylic acid esters of formula (VI-2) are obtained from a trans-4-hydroxy-cyclohexanecarboxylic acid ester of formula (IV-2).

General scheme E

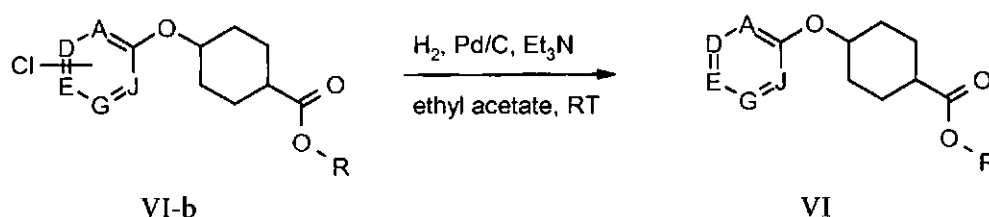


General scheme E:

Compounds of formula (VI-a) (compounds of formula (VI) in which R¹ is heteroaryl) can be prepared from a 4-hydroxy-cyclohexanecarboxylic acid ester of formula (IV) and a heteroaryl chloride of formula (VII) in the presence of a catalytic or stoichiometric amount of sodium

- 5 methanesulfinate and a base such as potassium carbonate in DMF at 120 °C or in the presence of a catalyst system formed from cuprous iodide and 1,10-phenanthroline and a base such as cesium carbonate in toluene at reflux.

General scheme F

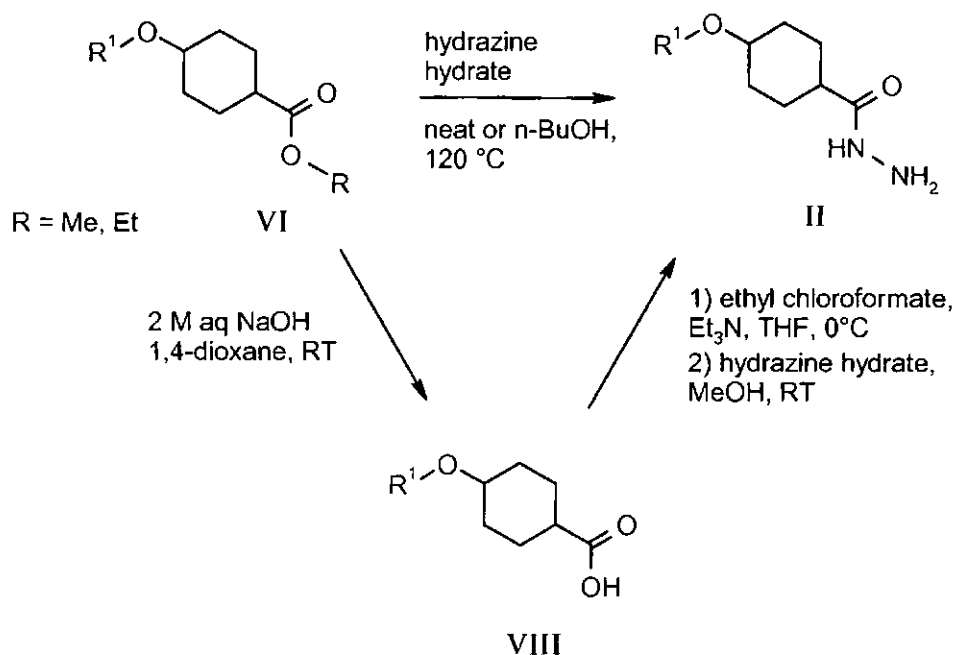


R = Me, Et

10 **General scheme F:**

Compounds of formula (VI-b) (compounds of formula (VI) in which R¹ is substituted with Cl) can be dechlorinated under hydrogenolytic conditions in the presence of palladium on charcoal and triethylamine in ethyl acetate at room temperature.

General scheme G



General scheme G:

A 4-aryloxy-cyclohexanecarboxylic acid ester of formula (VI) can be converted to a hydrazide derivative of formula (II) by heating with hydrazine hydrate. Alternatively, an ester derivative of formula (VI) can be hydrolyzed to a carboxylic acid derivative of formula (VIII) using a biphasic mixture of aqueous sodium or potassium hydroxide solution and an ethereal solvent such as dioxane. A hydrazide derivative of formula (II) can be obtained by activating an acid intermediate of formula (VIII), e.g. with ethyl chloroformate, thionyl chloride, oxalylchloride or a peptide coupling reagent, and subsequent coupling with hydrazine.

10 The compounds of the present invention exhibit V1a activity. They are selective inhibitors of the V1a receptor and are therefore likely to have a low potential to cause unwanted off-target related side-effects. The V1a activity may be detected as described below:

V1a activity

Material & Method:

15 The human V1a 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 V1a receptor binding studies were performed. Cell membranes were prepared from HEK293 cells transiently transfected with the expression vector and grown in 20 liter fermenters with the following protocol.

50g of cells are resuspended in 30ml freshly prepared ice cold Lysis buffer (50mM HEPES, 1mM EDTA, 10mM MgCl₂ adjusted to pH= 7.4 + complete cocktail of protease inhibitor (Roche Diagnostics)). Homogenized with Polytron for 1min and sonicated on ice for 2x 2 minutes at 80% intensity (Vibracell sonicator). The preparation is centrifuged 20 min at 500 g at 4°C, the pellet is discarded and the supernatant centrifuged 1hour at 43'000g at 4°C (19'000rpm). The pellet is resuspended in 12.5 ml Lysis 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 (Amersham) are mixed with an aliquot of membrane in binding buffer (50 mM Tris, 120mM NaCl, 5 mM KCl, 2 mM CaCl₂, 10 mM MgCl₂) 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%DMSO. 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 IC 50 the curve is fitted using a non-linear regression model (XLfit) and the K_i is calculated using the Cheng-Prussoff equation.

20

The following representative data show the antagonistic activity against human V1a receptor of compounds according to present invention:

Table II:

Ex#	pKi (hV1a)	Ex#	pKi (hV1a)	Ex#	pKi (hV1a)	Ex#	pKi (hV1a)
1	8.49	19	8.51	45	8.44	69	8.96
2	8.36	20	8.11	46	8.54	70	8.04
3	8.80	22	8.05	47	8.92	72	8.62
4	8.85	23	8.04	48	9.10	74	7.95
5	8.77	26	8.38	49	8.15	75	8.55
6	8.80	28	8.51	51	8.43	79	8.59
7	8.77	29	8.33	52	8.46	80	7.90
8	8.70	30	8.48	54	8.41	82	8.26
9	8.74	31	8.68	55	8.03	83	8.39
10	8.68	34	8.57	57	8.24	85	8.12
11	8.26	35	8.31	61	8.82	86	8.46
13	8.27	36	8.12	63	8.34	89	7.91
14	8.03	37	8.77	64	8.02	92	8.62
16	8.54	38	7.74	66	8.04	93	8.10
17	8.43	43	8.21	67	8.48	95	8.04
18	8.02	44	8.47	68	8.21		

The compounds of formula I as well as their pharmaceutically usable acid addition 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, dragées, hard and soft gelatine 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 usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragées and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules. Suitable excipients for soft gelatine 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 general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

The following examples illustrate the present invention without limiting it. All temperatures are given in degrees Celsius.

Example A

Tablets of the following composition are manufactured in the usual manner:

	<u>mg/tablet</u>
Active substance	5
Lactose	45
Corn starch	15
Microcrystalline cellulose	34
Magnesium stearate	1
Tablet weight	100

Example B

Capsules of the following composition are manufactured:

	<u>mg/capsule</u>
Active substance	10
Lactose	155
Corn starch	30
Talc	5
Capsule fill weight	200

The active substance, 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 is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelatine capsules.

Example C

5 Suppositories of the following composition are manufactured:

	<u>mg/supp.</u>
Active substance	15
Suppository mass	1285
Total	1300

10 The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45 °C. Thereupon, the finely powdered active substance 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.

15 The following examples 1 – 69 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.

EXAMPLES

20

4-Hydroxy-cyclohexanecarboxylic acid ester intermediates of formula (IV)

4-Hydroxy-cyclohexanecarboxylic acid ester 1

cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

25 A solution of cis-4-hydroxy-cyclohexanecarboxylic acid (10.0 g, 69.4 mmol) and 30 drops of concentrated sulfuric acid in methanol (700 ml) was heated at reflux over night. After cooling to room temperature solid sodium carbonate (0.15 g, 1.4 mmol) was added. The mixture was stirred for 30 min, filtered and concentrated in vacuo. The residue was triturated in ethyl acetate (150ml). The solids were removed by filtration. The filtrate was concentrated in vacuo to give
30 the crude product (10.3 g, 94%) as colorless oil, which was used in the following steps without further purification.
MS m/e: 159 (M+H⁺).

4-Hydroxy-cyclohexanecarboxylic acid ester 2

trans-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as a colorless oil in 63% yield according to the procedure described for the preparation of cis-4-hydroxy-cyclohexanecarboxylic acid methyl ester using
5 trans-4-hydroxy-cyclohexanecarboxylic acid instead of cis-4-hydroxy-cyclohexanecarboxylic acid.

MS (EI) m/e: 159 (M^+ , 1%), 140 ($M^+ - H_2O$, 45%)

4-Aryloxy-cyclohexanecarboxylic acid ester intermediates of formula (VI)

General procedure I: Etherification under Mitsunobu conditions

To a solution of triphenylphosphine (1.2 eq) in dry tetrahydrofuran (0.1 M) is added diethyl azodicarboxylate (1.2 eq) at 0 °C. After 20 min a phenol derivative of formula (V) (1.2 eq) and a solution of a 4-hydroxy-cyclohexanecarboxylic acid ester of formula (IV) in tetrahydrofuran (1-3
15 M) are added consecutively at 5 °C. After completed addition the cooling bath is removed and the reaction mixture is allowed to warm to room temperature and stirred for 3-18 h. The solvent is evaporated and the residue is dissolved in ethyl acetate. The ethyl acetate solution is washed with one to two portions of 1 M aqueous sodium hydroxide solution. The aqueous layer is extracted with one to two portions of ethyl acetate. The combined organic layers are dried over
20 anhydrous sodium sulfate and concentrated in vacuo. Purification by flash-chromatography gives a 4-aryloxy-cyclohexanecarboxylic acid ester of formula (VI).

General procedure II: Sodium methanesulfinate mediated arylation

To a solution of a 4-hydroxy-cyclohexanecarboxylic acid ester of formula (IV) (1 eq) and a heteroaryl chloride derivative (1 eq) in dry N,N-dimethylformamide (1 M) are added
25 consecutively sodium methanesulfinate (85%, 0.25 - 1 eq) and potassium carbonate (1.5 eq). After completed addition the reaction mixture is stirred at 120 °C for 3-18 h. After cooling to room temperature the reaction mixture is partitioned between tert-butyl methyl ether and water. The layers are separated and the aqueous layer is extracted with one to two portions of tert-butyl methyl ether. The combined organic layers are washed with one to two portions of water, dried
30 over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash-chromatography gives a 4-heteroaryloxy-cyclohexanecarboxylic acid ester of formula (VI-a).

General procedure III: Copper catalyzed arylation

To a mixture of cuprous iodide (0.1 eq), 1,10-phenanthroline (0.2 eq) and a heteroaryl chloride derivative (1 eq) in toluene (2 M) are added a 4-hydroxy-cyclohexanecarboxylic acid ester of formula (IV) (1 eq) and cesium carbonate (2 eq). The reaction mixture is heated at reflux for 20 h.

- 5 After cooling to room temperature the reaction mixture is partitioned between ethyl acetate and water. The layers are separated and the aqueous layer is extracted with one to two portions of ethyl acetate. The combined organic layers are washed with one to two portions of 0.5 aqueous hydrogen chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash-chromatography gives a 4-heteroaryloxy-cyclohexanecarboxylic acid ester
10 of formula (VI-a).

4-Aryloxy-cyclohexanecarboxylic acid ester 1

trans-4-Phenoxy-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as colorless oil in 23% yield according to general procedure I.

- 15 Phenol: Phenol

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 234 (M^+)

20

4-Aryloxy-cyclohexanecarboxylic acid ester 2

cis-4-Phenoxy-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as colorless oil in 54% yield according to general procedure I.

Phenol: Phenol

4-Hydroxy-cyclohexanecarboxylic acid ester: trans-4-Hydroxy-cyclohexanecarboxylic acid

- 25 methyl ester

MS m/e: 234 (M^+)

4-Aryloxy-cyclohexanecarboxylic acid ester 3

trans-4-(4-Fluoro-phenoxy)-cyclohexanecarboxylic acid methyl ester

- 30 The title compound was obtained as pink oil in 29% yield according to general procedure I.

Phenol: 4-Fluorophenol

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 252 (M^+)

4-Aryloxy-cyclohexanecarboxylic acid ester 4

trans-4-(4-Cyano-phenoxy)-cyclohexanecarboxylic acid methyl ester

5 The title compound was obtained according to general procedure I.

Phenol: 4-Hydroxybenzonitrile

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 260 ($M+H^+$)

10

4-Aryloxy-cyclohexanecarboxylic acid ester 5

trans-4-(4-Trifluoromethyl-phenoxy)-cyclohexanecarboxylic acid methyl ester

The title compound was obtained according to general procedure I.

Phenol: 4-Trifluoromethyl-phenol

15 4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 303 ($M+H^+$)

4-Aryloxy-cyclohexanecarboxylic acid ester 6

20 **trans-4-(3-Chloro-phenoxy)-cyclohexanecarboxylic acid methyl ester**

The title compound was obtained as colorless oil in 38% yield according to general procedure I

Phenol: 3-Chlorophenol

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

25 MS m/e: 268 (M^+)

4-Aryloxy-cyclohexanecarboxylic acid ester 7

trans-4-(3-Methoxy-phenoxy)-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as pink oil in 33% yield according to general procedure I.

30 Phenol: 3-Methoxyphenol

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 265 ($M+H^+$)

4-Aryloxy-cyclohexanecarboxylic acid ester 8

trans-4-(3-Cyano-phenoxy)-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as white solid in 29% yield according to general procedure I.

5 Phenol: 3-Hydroxypyridine

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 259 ($M+H^+$)

10

4-Aryloxy-cyclohexanecarboxylic acid ester 9

trans-4-m-Tolyloxy-cyclohexanecarboxylic acid methyl ester

The title compound was obtained according to general procedure I.

Phenol: 3-Methylphenol

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

15

MS m/e: 248 (M^+)

4-Aryloxy-cyclohexanecarboxylic acid ester 10

trans-4-(3-tert-Butyl-phenoxy)-cyclohexanecarboxylic acid methyl ester

20 The title compound was obtained according to general procedure I.

Phenol: 3-tert-Butylphenol

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 291 ($M+H^+$)

25

4-Aryloxy-cyclohexanecarboxylic acid ester 11

trans-4-(3-Trifluoromethyl-phenoxy)-cyclohexanecarboxylic acid methyl ester

The title compound was obtained according to general procedure I.

Phenol: 3-Trifluoromethylphenol

30 4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 302 ($M+H^+$)

4-Aryloxy-cyclohexanecarboxylic acid ester 12

trans-4-(2-Fluoro-phenoxy)-cyclohexanecarboxylic acid methyl ester

The title compound can be obtained according to general procedure I.

Phenol: 4-Fluorophenol

- 5 4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

4-Aryloxy-cyclohexanecarboxylic acid ester 13

trans-4-(2-Cyano-phenoxy)-cyclohexanecarboxylic acid methyl ester

- 10 The title compound was obtained as pink solid in 34% yield according to general procedure I.

Phenol: 2-Hydroxybenzonitrile

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 260 ($M+H^+$)

15

4-Aryloxy-cyclohexanecarboxylic acid ester 14

trans-4-o-Tolyloxy-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as colorless oil in 15% yield according to general procedure I.

Phenol: 2-Methylphenol

- 20 4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 248 (M^+)

4-Aryloxy-cyclohexanecarboxylic acid ester 15

- 25 **trans-4-(3,5-Difluoro-phenoxy)-cyclohexanecarboxylic acid methyl ester**

The title compound was obtained as off-white solid in 22% yield according to general procedure I.

Phenol: 3,5-Difluorophenol

- 30 4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

4-Aryloxy-cyclohexanecarboxylic acid ester 16

trans-4-(Naphthalen-2-yloxy)-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as yellow solid in 20% yield according to general procedure I.

Phenol: 2-Naphthol

- 5 4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 284 (M^+)

4-Aryloxy-cyclohexanecarboxylic acid ester 17

- 10 **trans-4-(Naphthalen-1-yloxy)-cyclohexanecarboxylic acid methyl ester**

The title compound was obtained as yellow solid in 20% yield according to general procedure I.

Phenol: 1-Naphthol

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

- 15 MS m/e: 284 (M^+)

4-Aryloxy-cyclohexanecarboxylic acid ester 18

trans-4-(Pyridin-3-yloxy)-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as white solid in 25% yield according to general procedure I.

- 20 Phenol: 3-Hydroxypyridine

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 236 ($M+H^+$)

- 25 **4-Aryloxy-cyclohexanecarboxylic acid ester 19**

trans-4-(5-Chloro-pyridin-3-yloxy)-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as off-white solid in 29% yield according to general procedure I.

Phenol: 3-Chloro-5-hydroxypyridine

- 30 4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 270 ($M+H^+$)

4-Aryloxy-cyclohexanecarboxylic acid ester 20

trans-4-(Pyridin-2-yloxy)-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as light red solid in 36% yield according to general procedure I.

Phenol: 2-Hydroxypyridine

- 5 4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 236 ($M+H^+$)

4-Aryloxy-cyclohexanecarboxylic acid ester 21

- 10 **trans-4-(6-Chloro-pyridin-2-yloxy)-cyclohexanecarboxylic acid methyl ester**

The title compound was obtained according to general procedure I.

Phenol: 6-Chloro-pyridin-2-ol

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

- 15 MS m/e: 270 ($M+H^+$)

4-Aryloxy-cyclohexanecarboxylic acid ester 22

trans-4-(5-Chloro-pyridin-2-yloxy)-cyclohexanecarboxylic acid methyl ester

The title compound was obtained according to general procedure I.

- 20 Phenol: 5-Chloro-pyridin-2-ol

4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 270 ($M+H^+$)

- 25 **4-Aryloxy-cyclohexanecarboxylic acid ester 23**

trans-4-(2,6-Dimethyl-pyrimidin-4-yloxy)-cyclohexanecarboxylic acid methyl ester

The title compound was obtained as light yellow oil in 32% yield according to general procedure I.

Phenol: 2,4-Dimethyl-6-hydroxypyrimidine

- 30 4-Hydroxy-cyclohexanecarboxylic acid ester: cis-4-Hydroxy-cyclohexanecarboxylic acid methyl ester

MS m/e: 265 ($M+H^+$)

4-Aryloxy-cyclohexanecarboxylic acid ester 24

cis/trans-4-(Pyrimidin-2-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:2)

The title compound was obtained as yellow amorphous solid in 24% yield according to general procedure III.

5 Heteroaryl chloride: 2-Chloropyrimidine

4-Hydroxy-cyclohexanecarboxylic acid ester: cis/trans-4-Hydroxy-cyclohexanecarboxylic acid ethyl ester (2 :1)

MS m/e: 251 ($M+H^+$)

10 **4-Aryloxy-cyclohexanecarboxylic acid ester 25**

cis/trans-4-(Pyrazin-2-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:1)

The title compound was obtained as white solid in 15% yield according to general procedure II.

Heteroaryl chloride : 2-Chloropyrazine

4-Hydroxy-cyclohexanecarboxylic acid ester: cis/trans-4-Hydroxy-cyclohexanecarboxylic acid

15 ethyl ester ester (2 :1)

MS m/e: 251 ($M+H^+$)

4-Aryloxy-cyclohexanecarboxylic acid ester 26

cis/trans-4-(6-Chloro-pyrimidin-4-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:1)

20 The title compound was obtained as colorless oil in 38% yield according to general procedure III.

Heteroaryl chloride : 4,6-Dichloropyrimidine

4-Hydroxy-cyclohexanecarboxylic acid ester: cis/trans-4-Hydroxy-cyclohexanecarboxylic acid

ethyl ester ester (2 :1)

MS m/e: 284 (M^+)

25

4-Aryloxy-cyclohexanecarboxylic acid ester 27

cis/trans-4-(Pyrimidin-4-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:1)

To an argon purged solution of cis/trans-4-(6-chloro-pyrimidin-4-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:1) (1.05 g, 3.69 mmol) and triethylamine (0.52 ml, 3.69 mmol) in ethyl acetate
30 (37 ml) was added palladium on charcoal 10% (0.078 g). The reaction mixture was purged with hydrogen gas and stirred under an atmosphere of hydrogen gas for 16 h at room temperature. The catalyst and the ammonium salts were removed by filtration over Decalite. The filtrate was concentrated in vacuo to give the title compound (0.92 g) as light yellow oil in quantitative yield.

MS m/e: 251 ($M+H^+$).

4-Aryloxy-cyclohexanecarboxylic acid ester 28

cis/trans-4-(6-Chloro-pyridazin-3-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:1)

5 The title compound was obtained as white solid in 39% yield according to general procedure III.

Heteroaryl chloride : 3,6-Dichloropyridazine

4-Hydroxy-cyclohexanecarboxylic acid ester: cis/trans-4-Hydroxy-cyclohexanecarboxylic acid ethyl ester (2 :1)

MS m/e: 285 ($M+H^+$)

10

4-Aryloxy-cyclohexanecarboxylic acid ester 29

cis/trans-4-(Pyridazin-3-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:1)

To an argon purged solution of cis/trans-4-(6-chloro-pyridazin-3-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:1) (1.30 g, 4.57 mmol) and triethylamine (0.64 ml, 4.57 mmol) in ethyl acetate
15 (46 ml) was added palladium on charcoal 10% (0.097 g). The reaction mixture was purged with hydrogen gas and stirred under an atmosphere of hydrogen gas for 4 h at room temperature. The catalyst and the ammonium salts were removed by filtration over Decalite. The filtrate was concentrated in vacuo to give the title compound (1.09 g, 95%) as light yellow oil.

MS m/e: 251 ($M+H^+$)

20

4-Aryloxy-cyclohexanecarboxylic acid intermediates of formula (VIII)

4-Aryloxy-cyclohexanecarboxylic acid 1

25

cis/trans-4-(Pyrimidin-2-yloxy)-cyclohexanecarboxylic acid (1:2)

To a solution of cis/trans-4-(pyrimidin-2-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:2) (0.35 g, 1.4 mmol) in 1,4-dioxane (7 ml) was added 2 M aqueous sodium hydroxide solution (7.0 ml, 14 mmol). Stirring at room temperature for 16 h was followed by acidification to pH 2-3
30 with 0.5 M aqueous hydrogen chloride solution (50 ml) and extraction with three 100-ml portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give the title compound (0.26 g, 83%) as yellow oil.

MS m/e: 221 ($M-H^+$).

4-Aryloxy-cyclohexanecarboxylic acid 2

cis/trans-4-(Pyrimidin-4-yloxy)-cyclohexanecarboxylic acid (1:1)

To a solution of cis/trans-4-(pyrimidin-4-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:1) (0.90 g, 3.6 mmol) in 1,4-dioxane (18 ml) was added 2 M aqueous sodium hydroxide solution (18 ml, 36 mmol). Stirring at room temperature for 3 h was followed by acidification to pH 2-3 with 1 M aqueous hydrogen chloride solution (42 ml) and extraction with four 100-ml portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give the title compound (0.76 g, 95%) as white solid.

10 MS m/e: 221 ($M-H^+$).

4-Aryloxy-cyclohexanecarboxylic acid 3

cis/trans-4-(Pyridazin-3-yloxy)-cyclohexanecarboxylic acid (1:1)

To a solution of cis/trans-4-(pyridazin-3-yloxy)-cyclohexanecarboxylic acid ethyl ester (1:1) (1.05 g, 4.19 mmol) in 1,4-dioxane (21 ml) was added 2 M aqueous sodium hydroxide solution (21 ml, 42 mmol). Stirring at room temperature for 16 h was followed by acidification to pH 2-3 with 1 M aqueous hydrogen chloride solution (44 ml) and extraction with three 100-ml portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give the title compound (0.80 g, 86%) as off-white solid.

20 MS m/e: 221 ($M-H^+$).

Hydrazide intermediates of formula (II)

General procedure IV: Conversion of ester to hydrazide

A mixture of 4-(aryloxy)-cyclohexanecarboxylic acid ester of formula (VI) (1 eq) and hydrazine hydrate (5 eq) is heated at 120 °C for 5 h. After cooling to room temperature the reaction mixture is partitioned between dichloromethane and water. The layers are separated and the organic layer is washed with water and brine. The organic layer is dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude title compound, which is used in the next step without further purification.

30

Hydrazide 1

trans-4-Phenoxy-cyclohexanecarboxylic acid hydrazide

A mixture of trans-4-phenoxy-cyclohexanecarboxylic acid methyl ester (1.07 g, 4.57 mmol) and hydrazine hydrate (0.22 g, 4.48 mmol) was heated at 120 °C for 4 h. After cooling to room

temperature the reaction mixture was concentrated in vacuo to give the crude title compound as white solid in quantitative yield, which was used in the next step without further purification.

MS m/e: 235 ($M+H^+$).

Hydrazide 2

5 **cis-4-Phenoxy-cyclohexanecarboxylic acid hydrazide**

A mixture of cis-4-phenoxy-cyclohexanecarboxylic acid methyl ester (0.55 g, 2.3 mmol) and hydrazine hydrate (0.11 g, 2.3 mmol) was heated at 120 °C for 24 h. After cooling to room temperature the reaction mixture was suspended in toluene (70 ml). After evaporation of the solvent, the residue was suspended in toluene (70 ml) again. The solvent was evaporated and the
10 residue was dried in high vacuo (1-2 mbar) to give the crude title compound (0.50 g, 92%) as light yellow foam, which was used in the next step without further purification.

MS m/e: 235 ($M+H^+$).

Hydrazide 3

trans-4-(4-Fluoro-phenoxy)-cyclohexanecarboxylic acid hydrazide

15 A mixture of trans-4-(4-fluoro-phenoxy)-cyclohexanecarboxylic acid methyl ester (0.23 g, 0.93 mmol) and hydrazine hydrate (0.046 g, 0.91 mmol) was heated at 120 °C for 3.5 h. After cooling to room temperature the reaction mixture was suspended in toluene (70 ml). After evaporation of the solvent, the residue was suspended in toluene (70 ml) again. The solvent was evaporated and the residue was dried in high vacuo (1-2 mbar) to give the crude title compound (0.22 g, 96%) as
20 white solid, which was used in the next step without further purification.

MS m/e: 253 ($M+H^+$).

Hydrazide 4

trans-4-(4-Cyano-phenoxy)-cyclohexanecarboxylic acid hydrazide

The title compound was obtained from trans-4-(4-cyano-phenoxy)-cyclohexanecarboxylic acid
25 methyl ester according to general procedure IV.

MS m/e: 260 ($M+H^+$).

Hydrazide 5

trans-4-(4-Trifluoromethyl-phenoxy)-cyclohexanecarboxylic acid hydrazide

The title compound was obtained from trans-4-(4-trifluoromethyl-phenoxy)-
30 cyclohexanecarboxylic acid methyl ester according to general procedure IV.

MS m/e: 303 ($M+H^+$)

Hydrazide 6

trans-4-(3-Chloro-phenoxy)-cyclohexanecarboxylic acid hydrazide

A mixture of trans-4-(3-chloro-phenoxy)-cyclohexanecarboxylic acid methyl ester (0.25 g, 0.93 mmol) and hydrazine hydrate (0.044 ml, 0.91 mmol) was heated at 120 °C for 22 h. Addition of
5 further hydrazine hydrate (0.020 ml, 0.42 mmol) was followed by stirring at 120 °C for 5 h. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (50 ml) and 1 M aqueous sodium hydroxide solution (50 ml). The layers were separated and the aqueous layer was extracted with a 50-ml portion of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude title
10 compound (0.21 g, 86%) as white solid, which was used in the next step without further purification.

MS m/e: 269 (M+H⁺)

Hydrazide 7

trans-4-(3-Methoxy-phenoxy)-cyclohexanecarboxylic acid hydrazide

15 A mixture of trans-4-(3-methoxy-phenoxy)-cyclohexanecarboxylic acid methyl ester (0.20 g, 0.75 mmol) and hydrazine hydrate (0.035 ml, 0.73 mmol) was heated at 120 °C for 22 h. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (50 ml) and 1 M aqueous sodium hydroxide solution (50 ml). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude title compound (0.18
20 g, 92%) as white solid, which was used in the next step without further purification.

MS m/e: 265 (M+H⁺)

Hydrazide 8

trans-4-(3-Cyano-phenoxy)-cyclohexanecarboxylic acid hydrazide

A mixture of trans-4-(3-cyano-phenoxy)-cyclohexanecarboxylic acid methyl ester (0.277 g, 1.07
25 mmol) and hydrazine hydrate (0.104 ml, 2.14 mmol) in n-butanol (0.5 ml) was heated at 120 °C for 18 h. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (50 ml) and 1 M aqueous sodium hydroxide solution (50 ml). The layers were separated and the aqueous layer was extracted with a 50-ml portion of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was
30 triturated in methanol (7 ml). The solids were removed by filtration and the filtrate was concentrated in vacuo to give the crude title compound (0.15 g, 55%) as light red solid, which was used in the next step without further purification.

MS m/e: 260 (M+H⁺)

Hydrazide 9

trans-4-m-Tolyloxy-cyclohexanecarboxylic acid hydrazide

The title compound was obtained from trans-4-m-tolyloxy-cyclohexanecarboxylic acid methyl ester according to general procedure IV.

5 MS m/e: 249 ($M+H^+$)

Hydrazide 10

trans-4-(3-tert-Butyl-phenoxy)-cyclohexanecarboxylic acid hydrazide

The title compound was obtained from trans-4-(3-tert-butyl-phenoxy)-cyclohexanecarboxylic acid methyl ester according to general procedure IV.

10 Hydrazide 11

trans-4-(3-Trifluoromethyl-phenoxy)-cyclohexanecarboxylic acid hydrazide

The title compound was obtained from trans-4-(3-trifluoromethyl-phenoxy)-cyclohexanecarboxylic acid methyl ester according to general procedure IV.

MS m/e: 303 ($M+H^+$)

15 Hydrazide 12

trans-4-(2-Fluoro-phenoxy)-cyclohexanecarboxylic acid hydrazide

The title compound was obtained from trans-4-(2-fluoro-phenoxy)-cyclohexanecarboxylic acid methyl ester according to general procedure IV.

Hydrazide 13

20 **trans-4-(2-Cyano-phenoxy)-cyclohexanecarboxylic acid hydrazide**

A mixture of trans-4-(2-cyano-phenoxy)-cyclohexanecarboxylic acid methyl ester (0.20 g, 0.77 mmol) and hydrazine hydrate (0.037 ml, 0.76 mmol) in n-butanol (0.5 ml) was heated at 120 °C for 22 h. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (50 ml) and 1 M aqueous sodium hydroxide solution (50 ml). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude title compound (0.18 g, 90%) as white solid, which was used in the next step without further purification.

25 MS m/e: 260 ($M+H^+$)

Hydrazide 14

30 **trans-4-o-Tolyloxy-cyclohexanecarboxylic acid hydrazide**

A mixture of trans-4-o-tolyloxy-cyclohexanecarboxylic acid methyl ester (0.091 g, 0.36 mmol) and hydrazine hydrate (0.02 ml, 0.36 mmol) was heated at 120 °C for 22 h. After cooling to room temperature the reaction mixture was suspended in toluene. After evaporation of the

solvent the residue was dried in high vacuo (1-2 mbar) to give the crude title compound (0.73 g, 81%) as white solid, which was used in the next step without further purification.

MS m/e: 249 ($M+H^+$)

Hydrazide 15

5 **trans-4-(3,5-Difluoro-phenoxy)-cyclohexanecarboxylic acid hydrazide**

A mixture of trans-4-(3,5-difluoro-phenoxy)-cyclohexanecarboxylic acid methyl ester (0.148 g, 0.548 mmol) and hydrazine hydrate (0.106 ml, 2.19 mmol) was heated at 120 °C for 18 h. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (50 ml) and 1 M aqueous sodium hydroxide solution (50 ml). The organic layer was separated. The aqueous layer was extracted with one portion of ethyl acetate (50 ml). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude title compound (0.14 g, 96%) as light yellow solid, which was used in the next step without further purification.

MS m/e: 271 ($M+H^+$)

15 **Hydrazide 16**

trans-4-(Naphthalen-2-yloxy)-cyclohexanecarboxylic acid hydrazide

A mixture of trans-4-(naphthalen-2-yloxy)-cyclohexanecarboxylic acid methyl ester (0.130 g, 0.457 mmol) and hydrazine hydrate (0.02 ml, 0.45 mmol) in methanol (0.5 ml) was heated at 80 °C for 16 h. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (50 ml) and 1 M aqueous sodium hydroxide solution (50 ml). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude title compound (0.112 g, 86%) as yellow solid, which was used in the next step without further purification.

MS m/e: 285 ($M+H^+$)

25 **Hydrazide 17**

trans-4-(Naphthalen-1-yloxy)-cyclohexanecarboxylic acid hydrazide

A mixture of trans-4-(naphthalen-1-yloxy)-cyclohexanecarboxylic acid methyl ester (0.130 g, 0.457 mmol) and hydrazine hydrate (0.022 ml, 0.45 mmol) in methanol (0.5 ml) was heated at 80 °C for 16 h. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (50 ml) and 1 M aqueous sodium hydroxide solution (50 ml). The organic layer was separated. 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 in vacuo to give a 3:1 mixture of the crude title compound and starting material. This mixture (0.12 g) and

hydrazine hydrate (0.022 ml, 0.45 mmol) were dissolved in 1,4-dioxane (0.4 ml) and heated at reflux for 18 h. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (50 ml) and 1 M aqueous sodium hydroxide solution (50 ml). The organic layer was separated. 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 in vacuo to give the crude title compound (0.120 g, 83%) as yellow solid with a purity of 90%, which was used in the next step without further purification.

MS m/e: 285 (M+H⁺)

Hydrazide 18

10 **trans-4-(Pyridin-3-yloxy)-cyclohexanecarboxylic acid hydrazide**

A mixture of trans-4-(pyridin-3-yloxy)-cyclohexanecarboxylic acid methyl ester (0.141 g, 0.599 mmol) and hydrazine hydrate (0.029 ml, 0.59 mmol) in n-butanol (0.5 ml) was heated at 120 °C for 22 h. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (50 ml) and 1 M aqueous sodium hydroxide solution (50 ml). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude title compound (0.061 g, 43%) as white solid, which was used in the next step without further purification.

MS m/e: 236 (M+H⁺)

Hydrazide 19

20 **trans-4-(5-Chloro-pyridin-3-yloxy)-cyclohexanecarboxylic acid hydrazide**

A mixture of trans-4-(5-chloro-pyridin-3-yloxy)-cyclohexanecarboxylic acid methyl ester (0.19 g, 0.70 mmol) and hydrazine hydrate (0.14 ml, 2.8 mmol) in n-butanol (0.5 ml) was heated at 120 °C for 18 h. After cooling to room temperature the reaction mixture was triturated in toluene (100 ml). The product was collected by filtration and dried in vacuo to give the crude title compound (0.15 g, 79%) as white solid, which was used in the next step without further purification.

MS m/e: 270 (M+H⁺)

Hydrazide 20

trans-4-(Pyridin-2-yloxy)-cyclohexanecarboxylic acid hydrazide

30 A mixture of trans-4-(pyridin-2-yloxy)-cyclohexanecarboxylic acid methyl ester (1.33 g, 5.66 mmol) and hydrazine hydrate (0.55 ml, 11 mmol) in n-butanol (1 ml) was heated at 120 °C for 68 h. After cooling to room temperature the reaction mixture was evaporated and dried in high

vacuo (ca. 1-2 mbar) at 100 °C for 2 h to give the crude title compound (1.28 g, 96%) as white solid, which was used in the next step without further purification.

MS m/e: 236 ($M+H^+$)

Hydrazide 21

5 **trans-4-(6-Chloro-pyridin-2-yloxy)-cyclohexanecarboxylic acid hydrazide**

The title compound was obtained from trans-4-(6-chloro-pyridin-2-yloxy)-cyclohexanecarboxylic acid methyl ester according to general procedure IV.

MS m/e: 270 ($M+H^+$)

Hydrazide 22

10 **trans-4-(5-Chloro-pyridin-2-yloxy)-cyclohexanecarboxylic acid hydrazide**

The title compound was obtained from trans-4-(5-chloro-pyridin-2-yloxy)-cyclohexanecarboxylic acid methyl ester according to general procedure IV.

Hydrazide 23

trans-4-(2,6-Dimethyl-pyrimidin-4-yloxy)-cyclohexanecarboxylic acid hydrazide

15 A mixture of trans-4-(2,6-dimethyl-pyrimidin-4-yloxy)-cyclohexanecarboxylic acid methyl ester (0.20 g, 0.76 mmol) and hydrazine hydrate (0.15 ml, 3.0 mmol) in n-butanol (0.5 ml) was heated at reflux over night. The reaction mixture was evaporated and dried in high vacuo (ca. 1-2 mbar) to give the crude title compound (0.19 g, 95%) as white solid, which was used in the next step without further purification.

20 MS m/e: 265 ($M+H^+$)

Hydazide 24

cis/trans-4-(Pyrimidin-2-yloxy)-cyclohexanecarboxylic acid hydrazide (1:2)

To a solution of cis/trans-4-(pyrimidin-2-yloxy)-cyclohexanecarboxylic acid (1:2) (0.258 g, 1.16 mmol) and triethylamine (0.162 ml, 1.16 mmol) in THF (6 ml) was added ethyl chloroformate
25 (0.111 ml, 1.16 mmol) at 0 °C. The reaction mixture was stirred for 1 h. The ammonium salts were removed by filtration. The filtrate was added to a cold solution of hydrazine hydrate (0.116 g, 2.32 mmol) in methanol (10 ml). The reaction mixture was stirred for 2 h at room temperature and then partitioned between ethyl acetate (50 ml) and a mixture of a 1:1 mixture of 1 M aqueous sodium hydroxide solution and brine (50 ml). The layers were separated. The aqueous
30 layer was extracted with five 50-ml portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude title compound (0.177 g, 65%) as white solid, which was used in the next step without further purification.

MS m/e: 237 ($M+H^+$)

Hydrazide 25

trans-4-(Pyrazin-2-yloxy)-cyclohexanecarboxylic acid hydrazide

A mixture of cis/trans-4-(pyrazin-2-yloxy)-cyclohexanecarboxylic acid ethyl ester (1.11 g, 4.41 mmol) and hydrazine hydrate (0.442 g, 8.83 mmol) was heated at 120 °C for 72 h. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (50 ml) and water (30 ml). The organic layer was separated. The aqueous layer was extracted with two 50-ml portions of ethyl acetate. The combined organic layers were washed with brine (30 ml), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude cis/trans-hydrazide was triturated in ethyl acetate (5 ml). The precipitate was collected by filtration and dried in vacuo to give the crude title compound (0.236 g, 23%) as white solid, which was used in the next step without further purification.

MS m/e: 237 (M+H⁺)

Hydrazide 26

cis/trans-4-(Pyrimidin-4-yloxy)-cyclohexanecarboxylic acid hydrazide (1:1)

To a solution of cis/trans-4-(pyrimidin-4-yloxy)-cyclohexanecarboxylic acid (1:1) (0.750 g, 3.37 mmol) and triethylamine (0.470 ml, 3.37 mmol) in THF (16 ml) was added ethyl chloroformate (0.322 ml, 3.37 mmol) at 0 °C. The reaction mixture was stirred for 1 h. The ammonium salts were removed by filtration. The filtrate was added to a cold solution of hydrazine hydrate (0.338 g, 6.75 mmol) in methanol (20 ml). The reaction mixture was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate (100 ml) and a 1:1 mixture of 1 M aqueous sodium hydroxide solution and brine (30 ml). The organic layer was separated. The aqueous layer was extracted with three 100-ml portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude title compound (0.588 g, 74%) as off-white solid, which was used in the next step without further purification.

MS m/e: 237 (M+H⁺)

Hydrazide 27

cis/trans-4-(Pyridazin-3-yloxy)-cyclohexanecarboxylic acid hydrazide (1:1)

To a solution of cis/trans-4-(pyridazin-3-yloxy)-cyclohexanecarboxylic acid (1:1) (0.780 g, 3.51 mmol) and triethylamine (0.489 ml, 3.37 mmol) in THF (17 ml) was added ethyl chloroformate (0.334 ml, 3.51 mmol) at 0 °C. The reaction mixture was stirred for 1 h. The ammonium salts were removed by filtration. The filtrate was added to a cold solution of hydrazine hydrate (0.351 g, 7.02 mmol) in methanol (20 ml). The reaction mixture was stirred for 2 h at room temperature.

The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate (100 ml) and a 1:1 mixture of 1 M aqueous sodium hydroxide solution and brine (30 ml). The organic layer was separated. The aqueous layer was extracted with five 75-ml portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude title compound (0.580 g, 70%) as off-white solid,

MS m/e: 237 ($M+H^+$)

Thiolactam intermediates of formula (III)

10 **7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester**

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 min 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 tert-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.

20 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 tert-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.

25 MS m/e: 273 ($M+H^+$).

c) [tert-Butoxycarbonyl-(5-chloro-2-nitro-benzyl)-amino]-acetic acid ethyl ester

30 A solution of (5-chloro-2-nitro-benzylamino)-acetic acid ethyl ester (110 g, 0.403 mol), di-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)-tert-butoxycarbonyl-amino]-acetic acid ethyl ester

- 5 To a solution of [tert-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 min. 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
- 10 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 ($M+H^+$).

15 e) 7-Chloro-2-oxo-1,2,3,5-tetrahydro-benzo[1,4]diazepine-4-carboxylic acid tert-butyl ester

- To a solution of [(2-amino-5-chloro-benzyl)-tert-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
- 20 by addition of water (400 ml), saturated aqueous ammonium chloride solution (280 ml) and ethyl acetate (800 ml). After 10 min the precipitate was collected by filtration. The organic layer was 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.

25 MS m/e: 295 ($M-H^+$).

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

- A mixture of 7-chloro-2-oxo-1,2,3,5-tetrahydro-benzo[1,4]diazepine-4-carboxylic acid tert-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
- 30 solvent was evaporated and the residue was triturated in tert-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 ($M-H^+$).

7-Fluoro-2-thioxo-1,2,3,5-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-

- 5 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⁺).

Examples

10 General procedure V: Condensation of hydrazide and thiolactam to triazole

A mixture of a hydrazide derivative 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 R² is tert-butoxycarbonyl) is used the N-tert-butoxycarbonyl group of the resulting triazole product of formula (I-a) may be partially or completely cleaved thermally, and a secondary amine derivative of formula (I-b) is obtained in addition or as the sole product.

General procedure VI: Cleavage of N-tert-butoxycarbonyl (N-BOC) group

- 20 A solution of an N-BOC derivative of general formula (I-a) (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 min. After cooling to room temperature the reaction mixture is concentrated in vacuo to give a secondary amine derivative of general formula (I-b) 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 (I-b).

General procedure VII: Reductive N-alkylation

- 30 A mixture of a compound of formula (I-b) 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 (I-b) 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 derivative of formula (I).

5

Example 1

trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white foam in 83% yield according to general procedure V.

Hydrazide: trans-4-Phenoxy-cyclohexanecarboxylic acid hydrazide

10 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 2

trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride

15

The title compound was obtained as white solid in 98% yield from trans-8-chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 395 (M+H⁺)

20

Example 3

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

The title compound was obtained as white solid in 64% yield from trans-8-chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and

25 paraformaldehyde according to general procedure VII.

MS m/e: 409 (M+H⁺).

Example 4

trans-1-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-ethanone

30 To a solution of trans-8-chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride (0.071 g, 0.18 mmol) and triethylamine (0.048 ml, 0.35 mmol) in dichloromethane was added acetyl chloride (0.013 ml, 0.18 mmol) at room temperature. Stirring for 18 h was followed by partitioning between 1 M aqueous sodium hydroxide solution (50 ml)

and dichloromethane (50 ml). The organic layer was separated. The aqueous layer was extracted with one 50-ml portion of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash-chromatography with n-heptane/ethyl acetate as eluent gave the title compound (0.039 g, 54%) as white solid.

5 MS m/e: 437 ($M+H^+$).

Example 5

trans-8-Chloro-5-methanesulfonyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

To a solution of trans-8-chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
10 benzoazulene hydrochloride (0.065 g, 0.15 mmol) and triethylamine (0.044 ml, 0.32 mmol) in dichloromethane (5 ml) was added methanesulfonyl chloride (0.013 ml, 0.17 mmol) at room temperature. After stirring for 20 h the reaction mixture was transferred directly onto a silica gel chromatography column. Elution with n-heptane/ethyl acetate gave the title compound (0.051 g, 72%) as white solid.

15 MS m/e: 473 ($M+H^+$).

Example 6

trans-2-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-ethanol

The title compound was obtained as white solid in 59% yield from trans-8-chloro-1-(4-phenoxy-
20 cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and glycolaldehyde according to general procedure VII.

MS m/e: 439 ($M+H^+$).

Example 7

trans-8-Chloro-5-isopropyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white solid in 45% yield from trans-8-chloro-1-(4-phenoxy-
cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and acetone according to general procedure VII.

MS m/e: 437 ($M+H^+$).

Example 8

trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-sulfonic acid dimethylamide

To a solution of trans-8-chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride (0.062 g, 0.14 mmol) and triethylamine (0.030 ml, 0.22 mmol) in dichloromethane (2.5 ml) was added N,N-dimethylsulfamoyl chloride (0.023 ml, 0.22 mmol) at room temperature. After stirring for 72 h the reaction mixture was transferred directly onto a silica gel chromatography column. Elution with n-heptane/ethyl acetate gave the title compound (0.042 g, 58%) as white solid.

10 MS m/e: 502 ($M+H^+$).

Example 9

trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-5-pyridin-2-ylmethyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

To a mixture of trans-8-chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride (0.064 g, 0.15 mmol) and potassium carbonate (0.062 ml, 0.45 mmol) in acetonitrile (1 ml) was added 2-(bromomethyl)pyridine hydrobromide (0.040 ml, 0.16 mmol) at room temperature. Stirring for 72 h at 50 °C was followed by partitioning between 1 M aqueous sodium hydroxide solution (50 ml) and dichloromethane (50 ml). The organic layer was separated. The aqueous layer was extracted with two 50-ml portions of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash-chromatography with n-heptane/ethyl acetate as eluent gave the title compound (0.044 g, 63%) as light brown solid.

20 MS m/e: 486 ($M+H^+$).

Example 10

trans-1-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-2-dimethylamino-ethanone

To a mixture of trans-8-chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride (0.179 g, 0.41 mmol) in tetrahydrofuran (2 ml) was added triethylamine (0.058 ml, 0.41 mmol). The suspension was stirred for 10 minutes. The ammonium salts were removed by filtration. The filtrate was concentrated in vacuo. The residue was redissolved in tetrahydrofuran (3 ml) followed by consecutive addition of N,N-dimethylglycine (0.056 g, 0.54 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.104 g, 0.54 mmol). Stirring for 18 h at 50 °C was followed by partitioning between water (50

ml) and dichloromethane (50 ml). The organic layer was separated. The aqueous layer was extracted with one 50-ml portion of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash-chromatography with n-heptane/ethyl acetate as eluent gave the title compound (0.057 g, 28%) as white solid.

5 MS m/e: 480 ($M+H^+$).

Example 11

trans-8-Fluoro-1-(4-phenoxy-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 54% yield according to general procedure V.

10 Hydrazide: trans-4-Phenoxy-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: 479 ($M+H^+$)

Example 12

trans-8-Fluoro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride

The title compound was obtained as light yellow solid in quantitative yield from trans-8-fluoro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

20 MS m/e: 379 ($M+H^+$)

Example 13

trans-8-Fluoro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white solid in 63% yield from trans-8-fluoro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and paraformaldehyde according to general procedure VII.

25 MS m/e: 393 ($M+H^+$).

Example 14

cis-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

30

The title compound was obtained as white solid in 69% yield according to general procedure V.

Hydrazide: cis-4-Phenoxy-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 15

5 **cis-8-Chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride**

The title compound was obtained as white solid in quantitative yield from cis-8-chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

10 MS m/e: 395 ($M+H^+$)

Example 16

cis-8-Chloro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white solid in 73% yield from cis-8-chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and

15 paraformaldehyde according to general procedure VII.

MS m/e: 409 ($M+H^+$)

Example 17

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

20

The title compound was obtained as white solid in 66% yield according to general procedure V. Hydrazide: trans-4-(4-Fluoro-phenoxy)-cyclohexanecarboxylic acid hydrazide

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

25 MS m/e: 513 ($M+H^+$)

Example 18

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

The title compound was obtained as white solid in quantitative yield from trans-8-chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

30

MS m/e: 413 ($M+H^+$)

Example 19

trans-8-Chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white solid in 70% yield from trans-8-chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 427 ($M+H^+$)

Example 20

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

The title compound was obtained according to general procedure V.

Hydrazide: trans-4-(4-Cyano-phenoxy)-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: 520 ($M+H^+$)

Example 21

trans-4-[4-(8-Chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-cyclohexyloxy]-benzonitrile hydrochloride

The title compound was obtained from trans-8-chloro-1-[4-(4-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 420 ($M+H^+$)

Example 22

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

The title compound was obtained from trans-4-[4-(8-chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-cyclohexyloxy]-benzonitrile hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 434 ($M+H^+$)

Example 23

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

The title compound was obtained according to general procedure V.

Hydrazide: trans-4-(4-Trifluoromethyl-phenoxy)-cyclohexanecarboxylic acid hydrazide

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

MS m/e: 563 ($M+H^+$)

5

Example 24

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

The title compound was obtained from trans-8-chloro-1-[4-(4-trifluoromethyl-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester

10 according to general procedure VI.

MS m/e: 463 ($M+H^+$)

Example 25

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

15 The title compound was obtained from trans-8-chloro-1-[4-(4-trifluoromethyl-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 477 ($M+H^+$)

Example 26

20 **trans-8-Chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester**

The title compound was obtained as white solid in 74% yield according to general procedure V.

Hydrazide: trans-4-(3-Chloro-phenoxy)-cyclohexanecarboxylic acid hydrazide

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

MS m/e: 529 ($M+H^+$)

Example 27

trans-8-Chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride

30 The title compound was obtained in quantitative yield from trans-8-chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 429 ($M+H^+$)

Example 28

trans-8-Chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as colorless oil in 83% yield from trans-8-chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 443 ($M+H^+$)

Example 29

trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white foam in 75% yield according to general procedure V.

Hydrazide: trans-4-(3-Methoxy-phenoxy)-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: 525.5 ($M+H^+$)

Example 30

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

The title compound was obtained as white solid in quantitative yield from trans-8-chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 425 ($M+H^+$)

Example 31

trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white solid in 43% yield from trans-8-chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 439 ($M+H^+$)

Example 32

trans-8-Chloro-1-[4-(3-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as brown solid in 18% yield with a purity of approximately 80% by LC-MS according to general procedure V.

Hydrazide trans-4-(3-Cyano-phenoxy)-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: 520 ($M+H^+$)

Example 33

trans-3-[4-(8-Chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulen-1-yl)-cyclohexyloxy]-benzonitrile hydrochloride

The title compound was obtained as brown solid in 95% yield from trans-8-chloro-1-[4-(3-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 420 ($M+H^+$)

Example 34

trans-3-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulen-1-yl)-cyclohexyloxy]-benzonitrile

The title compound was obtained as yellow solid in 43% yield from trans-3-[4-(8-chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulen-1-yl)-cyclohexyloxy]-benzonitrile hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 434 ($M+H^+$)

Example 35

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

The title compound was obtained according to general procedure V.

Hydrazide: trans-4-m-Tolyloxy-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 36

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

The title compound was obtained trans-8-chloro-1-(4-m-tolyloxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 409 ($M+H^+$)

Example 37

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

10 The title compound was obtained from trans-8-chloro-1-(4-m-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 423.5 ($M+H^+$)

Example 38

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

The title compound was obtained according to general procedure V.

Hydrazide: trans-4-(3-tert-Butyl-phenoxy)-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: 551.5 ($M+H^+$)

Example 39

trans-1-[4-(3-tert-Butyl-phenoxy)-cyclohexyl]-8-chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride

25 The title compound was obtained trans-1-[4-(3-tert-butyl-phenoxy)-cyclohexyl]-8-chloro-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 451 ($M+H^+$)

Example 40

trans-1-[4-(3-tert-Butyl-phenoxy)-cyclohexyl]-8-chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene

The title compound was obtained from trans-1-[4-(3-tert-butyl-phenoxy)-cyclohexyl]-8-chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 465 ($M+H^+$)

Example 41

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

The title compound was obtained according to general procedure V.

Hydrazide: trans-4-(3-Trifluoromethyl-phenoxy)-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: 563 ($M+H^+$)

Example 42

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

The title compound was obtained from trans-8-chloro-1-[4-(3-trifluoromethyl-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 463 ($M+H^+$)

Example 43

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

The title compound was obtained according to general procedure V.

Hydrazide: trans-4-(2-Fluoro-phenoxy)-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: 513 ($M+H^+$)

Example 44

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

The title compound was obtained from trans-8-chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-

5 4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 413 ($M+H^+$)

Example 45

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

10

The title compound was obtained from trans-8-chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 427.5 ($M+H^+$)

15

Example 46

trans-8-Chloro-1-[4-(2-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white foam in 52% yield according to general procedure V.

Hydrazide: trans-4-(2-Cyano-phenoxy)-cyclohexanecarboxylic acid hydrazide

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

MS m/e: 520 ($M+H^+$)

Example 47

trans-2-[4-(8-Chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-cyclohexyloxy]-benzonitrile hydrochloride

25

The title compound was obtained as white solid in 99% yield from trans-8-chloro-1-[4-(2-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 420 ($M+H^+$)

30

Example 48

trans-2-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulen-1-yl)-cyclohexyloxy]-benzonitrile

The title compound was obtained as white solid in 50% yield from trans-2-[4-(8-chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-cyclohexyloxy]-benzonitrile hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 434 ($M+H^+$)

Example 49

trans-8-Chloro-1-(4-o-tolyloxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as yellow solid in 52% yield according to general procedure V. Hydrazide: trans-4-o-Tolyloxy-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 50

trans-8-Chloro-1-(4-o-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride

The title compound was obtained as light yellow solid in quantitative yield from trans-8-chloro-1-(4-o-tolyloxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 409 ($M+H^+$)

Example 51

trans-8-Chloro-5-methyl-1-(4-o-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as light yellow solid in 72% yield from trans-8-chloro-1-(4-o-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 423 ($M+H^+$)

Example 52

trans-8-Chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as light yellow solid in 58% yield according to general procedure V.

Hydrazide: **trans-4-(3,5-Difluoro-phenoxy)-cyclohexanecarboxylic acid hydrazide**

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

Example 53

trans-8-Chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride

The title compound was obtained as white solid in quantitative yield from trans-8-chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 431 ($M+H^+$)

Example 54

trans-8-Chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white solid in 39% yield from trans-8-chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 445 ($M+H^+$)

Example 55

trans-8-Chloro-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as yellow solid in 78% yield according to general procedure V.

Hydrazide: **trans-4-(Naphthalen-2-yloxy)-cyclohexanecarboxylic acid hydrazide**

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

MS m/e: 545 ($M+H^+$)

Example 56

trans-8-Chloro-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride

The title compound was obtained as white solid in quantitative yield from trans-8-chloro-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 445 ($M+H^+$)

Example 57

trans-8-Chloro-5-methyl-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white foam in 60% yield from trans-8-chloro-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 459 ($M+H^+$)

Example 58

trans-8-Chloro-1-[4-(naphthalen-1-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as yellow solid in 73% yield according to general procedure V.
Hydrazide: **trans-4-(Naphthalen-1-yloxy)-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: 545 ($M+H^+$)

Example 59

trans-8-Chloro-1-[4-(naphthalen-1-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white solid in 97% yield from trans-8-chloro-1-[4-(naphthalen-1-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 445 ($M+H^+$)

Example 60

trans-8-Chloro-5-methyl-1-[4-(naphthalen-1-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white foam in 73% yield from trans-8-chloro-1-[4-(naphthalen-1-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 459 (M+H⁺)

Example 61

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

The title compound was obtained as white foam in 51% yield according to general procedure V.

Hydrazide: trans-4-(Pyridin-3-yloxy)-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: 496 (M+H⁺)

Example 62

trans-8-Chloro-1-[4-(pyridin-3-yloxy)-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 trans-8-chloro-1-[4-(pyridin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 396 (M+H⁺)

Example 63

trans-8-Chloro-5-methyl-1-[4-(pyridin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white solid in 41% yield from trans-8-chloro-1-[4-(pyridin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene dihydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 410 (M+H⁺)

Example 64

trans-8-Chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white foam in 71% yield according to general procedure V.

Hydrazide: trans-4-(5-Chloro-pyridin-3-yloxy)-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: 530 ($M+H^+$)

5

Example 65

trans-8-Chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride

The title compound was obtained as white solid in quantitative yield from trans-8-chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid

10 tert-butyl ester according to general procedure VI.

MS m/e: 430 ($M+H^+$)

Example 66

trans-8-Chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

15 The title compound was obtained as white solid in 65% yield from trans-8-chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and paraformaldehyde according to general procedure VI.

MS m/e: 444 ($M+H^+$)

Example 67

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

The title compound was obtained as white foam in 77% yield according to general procedure V.

Hydrazide: trans-4-(Pyridin-2-yloxy)-cyclohexanecarboxylic acid hydrazide

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

25

MS m/e: 496 ($M+H^+$)

Example 68

trans-8-Chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride

30 The title compound was obtained as white solid in quantitative yield from trans-8-chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 396 ($M+H^+$)

Example 69

trans-8-Chloro-5-methyl-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white solid in 41% yield from trans-8-chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 410 ($M+H^+$)

Example 70

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

The title compound was obtained according to general procedure V.

Hydrazide: trans-4-(6-Chloro-pyridin-2-yloxy)-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: 530 ($M+H^+$)

Example 71

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

The title compound was from trans-8-chloro-1-[4-(6-chloro-pyridin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 430 ($M+H^+$)

Example 72

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

The title compound was obtained from trans-8-chloro-1-[4-(6-chloro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 444 ($M+H^+$)

Example 73

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

The title compound was obtained according to general procedure V.

Hydrazide: trans-4-(5-Chloro-pyridin-2-yloxy)-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: 530 ($M+H^+$)

5

Example 74

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

The title compound was obtained from trans-8-chloro-1-[4-(5-chloro-pyridin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester

10 according to general procedure VI.

MS m/e: 430 ($M+H^+$)

Example 75

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

15 The title compound was obtained from trans-8-chloro-1-[4-(5-chloro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 444 ($M+H^+$)

Example 76

trans-8-Chloro-1-[4-(2,6-dimethyl-pyrimidin-4-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester

The title compound was obtained as white foam in 64% yield according to general procedure V.

Hydrazide: trans-4-(2,6-Dimethyl-pyrimidin-4-yloxy)-cyclohexanecarboxylic acid hydrazide

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

25

MS m/e: 525.5 MS ($M+H^+$)

Example 77

trans-8-Chloro-1-[4-(2,6-dimethyl-pyrimidin-4-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride

30 The title compound was obtained as white solid in quantitative yield from trans-8-chloro-1-[4-(2,6-dimethyl-pyrimidin-4-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 425 ($M+H^+$)

Example 78

trans-8-Chloro-1-[4-(2,6-dimethyl-pyrimidin-4-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene

The title compound was obtained as white solid in 15% yield from trans- 8-chloro-1-[4-(2,6-dimethyl-pyrimidin-4-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 439 (M+H⁺)

Example 79

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

Example 80

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

trans-8-Chloro-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester and cis-8-chloro-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester were obtained after separation by flash-column chromatography according to general procedure V.

Hydrazide: cis/trans-4-(Pyrimidin-2-yloxy)-cyclohexanecarboxylic acid hydrazide (1:2)

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

trans-8-Chloro-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester was obtained as off-white solid in 38% yield.
MS m/e: 497 (M+H⁺)

cis-8-Chloro-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester was obtained as off-white solid in 8% yield.

MS m/e: 497 (M+H⁺)

Example 81

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

The title compound was obtained as yellow solid in 73% yield from trans-8-chloro-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 397 ($M+H^+$)

Example 82

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

- 5 The title compound was obtained as white solid in 34% yield from trans-8-chloro-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure VII.

MS m/e: 411 ($M+H^+$)

Example 83

- 10 **trans-8-Chloro-1-[4-(pyrazin-2-yloxy)-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 70% yield according to general procedure V.

Hydrazide: trans-4-(Pyrazin-2-yloxy)-cyclohexanecarboxylic acid hydrazide

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

MS m/e: 497 ($M+H^+$)

Example 84

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

- 20 The title compound was obtained as yellow solid in 84% yield from trans-8-chloro-1-[4-(pyrazin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 397 ($M+H^+$)

Example 85

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

The title compound was obtained as white solid in 45% yield from trans 8-chloro-1-[4-(pyrazin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene and paraformaldehyde according to general procedure VII.

- 30 MS m/e: 411 ($M+H^+$)

Example 86

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

and

Example 87

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

- 5 trans-8-Chloro-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester and cis-8-chloro-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester were obtained after separation by flash-column chromatography according to general procedure V. Hydrazide: cis/trans-4-(Pyrimidin-4-yloxy)-cyclohexanecarboxylic acid hydrazide (1:1)
- 10 Thiolactam: 7-Chloro-2-thioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepine-4-carboxylic acid tert-butyl ester
- trans-8-Chloro-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester was obtained as white solid in 24% yield. MS m/e: 497 ($M+H^+$)
- 15 cis-8-Chloro-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester was obtained as white solid in 23% yield according to general procedure V. MS m/e: 497 ($M+H^+$)

Example 88

20 **trans-8-Chloro-1-[4-(pyrimidin-4-yloxy)-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 trans-8-chloro-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

- 25 MS m/e: 397 ($M+H^+$)

Example 89

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

The title compound was obtained as white solid in 29% yield from trans-8-chloro-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

- 30 MS m/e: 411 ($M+H^+$)

Example 90

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

The title compound was obtained as white solid in quantitative yield from cis-8-chloro-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 397 (M+H⁺)

Example 91

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

The title compound was obtained as white solid in 28% yield from cis-8-chloro-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 411 (M+H⁺)

Example 92

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

Example 93

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

trans-8-Chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester and cis-8-chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester were obtained after separation by flash-column chromatography according to general procedure V.

Hydrazide: cis/trans-4-(Pyridazin-3-yloxy)-cyclohexanecarboxylic acid hydrazide (1:1)

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

trans-8-Chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester was obtained as white solid in 19% yield.

MS m/e: 497 (M+H⁺)

cis-8-Chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester was obtained as white solid in 23% yield.

MS m/e: 497 ($M+H^+$)

Example 94

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

- 5 The title compound was obtained as off-white solid in quantitative yield from trans-8-chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 397 ($M+H^+$)

Example 95

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

The title compound was obtained as white solid in 11% yield from trans-8-chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

- 15 MS m/e: 411 ($M+H^+$)

Example 96

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

- 20 The title compound was obtained as off-white solid in quantitative yield from cis-8-chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester according to general procedure VI.

MS m/e: 397 ($M+H^+$)

Example 97

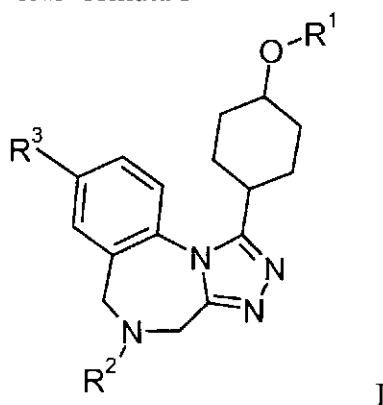
- 25 **cis-8-Chloro-5-methyl-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene**

The title compound was obtained as white solid in 3% yield from cis-8-chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride and paraformaldehyde according to general procedure VII.

MS m/e: 411 ($M+H^+$)

Claims

1. The compound of the general formula I



wherein

5 R¹ is aryl or heteroaryl, unsubstituted or substituted with one or more substituents independently selected from A;

R² is H,

C₁₋₁₂-alkyl, unsubstituted or substituted with one or more OH, halo, cyano or C₁₋₁₂-alkoxy, -(CH₂)_q-R^a, wherein R^a is phenyl or 5- or 6-membered heteroaryl, each

10 unsubstituted or substituted with one or more substituents independently selected from A,

-(CH₂)_rNRⁱRⁱⁱ,

-C(O)-C₁₋₁₂-alkyl, wherein C₁₋₁₂-alkyl is unsubstituted or substituted with one or more OH, halo, cyano or C₁₋₁₂-alkoxy,

15 -C(O)(CH₂)_qOC(O)-C₁₋₁₂-alkyl,

-C(O)(CH₂)_qNRⁱRⁱⁱ,

-C(O)O-C₁₋₁₂-alkyl, wherein alkyl is unsubstituted or substituted with one or more OH, halo, cyano or C₁₋₁₂-alkoxy,

-S(O)₂-C₁₋₁₂-alkyl,

20 -S(O)₂NRⁱRⁱⁱ,

Rⁱ and Rⁱⁱ are each independently H, C₁₋₁₂-alkyl, or form together with the nitrogen to which they are bound a 3- to 7-membered heterocycloalkyl containing one or two heteroatoms selected from N, O or S, which heterocycloalkyl is unsubstituted or substituted by one or more substituents independently selected from B,

25 q is 1, 2, 3 or 4,

r is 2, 3 or 4,

A is halo, cyano, OH, C₁₋₇-alkyl, halo-C₁₋₇-alkyl, C₁₋₇-alkoxy, halo-C₁₋₇-alkoxy, or hydroxy-C₁₋₇-alkyl,

B is oxo, halo, OH, C₁₋₇-alkyl or C₁₋₇-alkoxy,

R³ is Cl or F,
or a pharmaceutically acceptable salt thereof.

2. The compound of formula I according to claim 1, wherein

R¹ is a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono- or bicyclic
5 aromatic ring,
a monovalent 5- or 6-membered aromatic monocyclic or 9- or 10-membered aromatic
bicyclic ring containing from one to four ring heteroatoms selected from N, O, or S,
the remaining ring atoms being C,
each unsubstituted or substituted with one or more substituents independently selected
10 from A; and
A is halo, cyano, OH, C₁₋₇-alkyl, halo-C₁₋₇-alkyl, C₁₋₇-alkoxy, halo-C₁₋₇-alkoxy,
hydroxy-C₁₋₇-alkyl.

3. The compound according to any one of claims 1 or 2, wherein

R² is H,
15 C₁₋₁₂-alkyl, unsubstituted or substituted with one or more OH,
-(CH₂)_q-R^a, wherein R^a is phenyl or 5- or 6-membered heteroaryl and q is 1, 2, 3 or 4,
preferably 1,
-C(O)-C₁₋₁₂-alkyl,
-C(O)(CH₂)_qNRⁱRⁱⁱ, wherein Rⁱ and Rⁱⁱ are each independently H or C₁₋₁₂-alkyl, preferably
20 C₁₋₁₂-alkyl, and q is 1, 2, 3 or 4, preferably 1,
-C(O)O-C₁₋₁₂-alkyl,
-S(O)₂-C₁₋₁₂-alkyl, or
-S(O)₂NRⁱRⁱⁱ, wherein Rⁱ and Rⁱⁱ are each independently H or C₁₋₁₂-alkyl, preferably
C₁₋₁₂-alkyl.

4. The compound according to any one of claims 1 to 3, wherein R³ is Cl.

5. The compound according to any one of claims 1 to 4, wherein the compound is
selected from

trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-
carboxylic acid tert-butyl ester,

30 trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene
hydrochloride,

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

- trans-1-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-ethanone,
- trans-8-Chloro-5-methanesulfonyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- 5 trans-2-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-ethanol,
- trans-8-Chloro-5-isopropyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-
- 10 sulfonic acid dimethylamide,
- trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-5-pyridin-2-ylmethyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- trans-1-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-2-dimethylamino-ethanone,
- 15 trans-8-Fluoro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
- trans-8-Fluoro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- cis-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-
- 20 carboxylic acid tert-butyl ester,
- cis-8-Chloro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- trans-8-Chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
- 25 trans-8-Chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride,
- trans-8-Chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- trans-8-Chloro-1-[4-(4-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
- 30 benzo[e]azulene-5-carboxylic acid tert-butyl ester,
- trans-4-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-cyclohexyloxy]-benzonitrile,
- trans-8-Chloro-1-[4-(4-trifluoromethyl-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
- 35 trans-8-Chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,

- trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzo[e]azulene hydrochloride,
5 trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-
2,3,5,10b-tetraaza-benzoazulene,
trans-3-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulen-1-yl)-
cyclohexyloxy]-benzonitrile,
trans-8-Chloro-1-(4-m-tolyloxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-
10 carboxylic acid tert-butyl ester,
trans-8-Chloro-1-(4-m-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzo[e]azulene hydrochloride,
trans-8-Chloro-5-methyl-1-(4-m-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzo[e]azulene,
15 trans-1-[4-(3-tert-Butyl-phenoxy)-cyclohexyl]-8-chloro-4H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-
20 benzo[e]azulene hydrochloride,
trans-8-Chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-
tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(2-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,
25 trans-2-[4-(8-Chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-
cyclohexyloxy]-benzonitrile hydrochloride,
trans-2-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulen-1-yl)-
cyclohexyloxy]-benzonitrile,
trans-8-Chloro-1-(4-o-tolyloxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-
30 carboxylic acid tert-butyl ester,
trans-8-Chloro-5-methyl-1-(4-o-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-
benzoazulene,
trans-8-Chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,
35 trans-8-Chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-
2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-
benzoazulene-5-carboxylic acid tert-butyl ester,

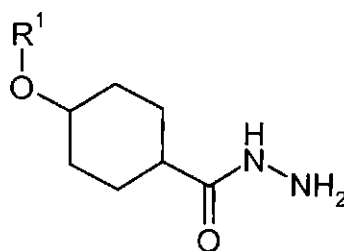
- trans-8-Chloro-5-methyl-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- trans-8-Chloro-1-[4-(pyridin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
- 5 trans-8-Chloro-5-methyl-1-[4-(pyridin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- trans-8-Chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- 10 trans-8-Chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride,
- 15 trans-8-Chloro-5-methyl-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
- trans-8-Chloro-1-[4-(6-chloro-pyridin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-1-[4-(6-chloro-pyridin-2-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
- 20 trans-8-Chloro-1-[4-(5-chloro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride,
- trans-8-Chloro-1-[4-(5-chloro-pyridin-2-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
- 25 trans-8-Chloro-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
- cis-8-Chloro-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-5-methyl-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
- 30 trans-8-Chloro-1-[4-(pyrazin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-5-methyl-1-[4-(pyrazin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
- 35 trans-8-Chloro-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
- trans-8-Chloro-5-methyl-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,

trans-8-Chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-

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

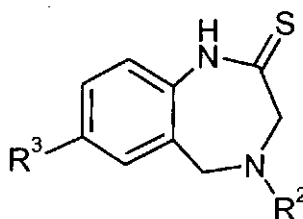
benzo[e]azulene-5-carboxylic acid tert-butyl ester, or
5 trans-8-Chloro-5-methyl-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.

6. A process for the preparation of the compound of formula I according to any of claims 1 to 5, comprising the step of reacting a compound of formula II



II

10 with a compound of formula (III):



III

to obtain a compound of formula (I) wherein R¹, R² and R³ are as defined in claim 1.

7. A compound formula I obtainable by the process according to claim 6.

15 8. A compound of formula I according to any one of claims 1 to 5 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.

20

9. A pharmaceutical composition comprising a compound of formula I according to any one of claims 1 to 5.

10. A pharmaceutical composition according to claim 9, 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,
5 schizophrenia, and aggressive behavior.

11. Use of a compound of formula I according to any one of claims 1 to 5 for the preparation of a medicament.

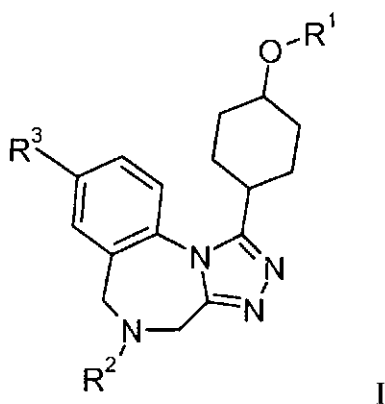
10 12. Use according to claim 11, wherein the medicament is useful for the prevention or treatment of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

15

13. The invention as described hereinabove.

Abstract

The present invention is concerned with arylcyclohexylethers of dihydro-tetraazabenzazulene derivatives, i.e. arylcyclohexylethers of 5,6-dihydro-4H-2,3,5,10b-tetraaza-
5 benzo[e]azulene derivatives of formula I



wherein R¹, R² and R³ are as described herein.

The compounds according to the invention act as V1a receptor modulators, and in particular as V1a receptor antagonists, their manufacture, pharmaceutical compositions
10 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.