(11) Application No. AU 2005293820 B2

(19) AUSTRALIAN PATENT OFFICE

(54) Title

Imidazo [1, 5-a]triazolo[1, 5-d]benzodiazepine derivatives for the treatment of cognitive disorders

(51)[6] International Patent Classification(s)

C07D 487/12 (2006.01)
A61K 31/5517 (2006.01)
A61P 25/00 (2006.01)
A61P 25/18 (2006.01)
A61P 25/22 (2006.01)
A61P 25/28 (2006.01)
A61P 43/00 (2006.01)
C07D 487/12 20060101AFI2010101 4BHAU **A61K** 31/5517 20060101ALI2010101 4BHAU **A61P** 25/00 20060101ALI2006042 0BHEP **A61P** 25/18 20060101ALI2006042 0BHEP **A61P** 25/22 20060101ALI2006042 0BHEP **A61P** 25/28 20060101ALI2006042 0BHEP **A61P** 43/00 20060101ALI2006042 0BHEP

(21) Application No: 2005293820 (22) Application Date: 2005.10.04

(87) WIPO No: WO06/040038

(30) Priority Data

(31) Number	(32) Date	(33) Country
04105000.6	2004.10.12	EP

(43) Publication Date : 2006.04.20

(71) Applicant(s)

F. Hoffmann-La Roche AG

(72) Inventor(s)

Stadler, Heinz; Thomas, Andrew William; Knust, Henner

(74) Agent/Attorney

Spruson & Ferguson, Level 35 St Martins Tower 31 Market Street, Sydney, NSW, 2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 April 2006 (20.04.2006)

PCT

(10) International Publication Number
WO 2006/040038 A1

(51) International Patent Classification:
A61K 31/5517 (2006.01) *A61P 25/22* (2006.01)
A61P 25/00 (2006.01) *A61P 25/28* (2006.01)
A61P 25/18 (2006.01) *A61P 43/00* (2006.01)

(21) International Application Number:
PCT/EP2005/010655

(22) International Filing Date: 4 October 2005 (04.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04105000.6 12 October 2004 (12.10.2004) EP

(71) Applicant *(for all designated States except US)*: **F.HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KNUST, Henner** [DE/DE]; Untere Dorfstrasse 20, 79618 Rheinfelden (DE). **STADLER, Heinz** [CH/CH]; Waldhofstrasse 37, CH-4310 Rheinfelden (CH). **THOMAS, Andrew, William** [GB/CH]; Zwinglistrasse 4, CH-4127 Birsfelden (CH).

(74) Agent: **POPPE, Regina**; Grenzacherstrasse 124, CH-4070 Basel (CH).

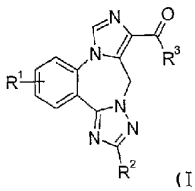
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZO [1, 5-A]TRIAZOLO[1, 5-D]BENZODIAZEPINE DERIVATIVES FOR TIIE TREATMENT OF COGNITIVE DISORDERS



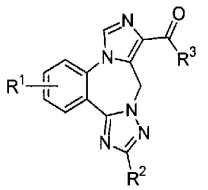
(I)

(57) Abstract: The present invention is concerned with the use of substituted imidazo [1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine derivatives of the following formula (I); wherein R^1 is halogen, lower alkyl, lower alkynyl, cycloalkyl, lower alkoxy, OCF_3, -NHR, - NHC(O)R or $-NHSO_2R$; R^2 is hydrogen, methyl or aryl, which is unsubstituted or substituted by one or two substituents, selected from the group consisting of halogen or lower alkoxy; R^3 is hydrogen, lower alkyl, lower alkenyl, cycloalkyl, lower alkoxy, $-O(CH_2)_{n1}$-Olower alkyl, $-(CH_2)_n$-aryl, which is optionally substituted by lower alkyl or halogen, heteroaryl, -NHR, $-NR_2$, wherein R_2 may be the same or different, or is - $NHCH_2C{=}CH$, or pyrrolidin-1-one; R is hydrogen, lower alkyl, lower alkyl substituted by halogen, heteroaryl, -(CH2)nO-lower alkyl, -NH-lower alkyl, cycloalkyl or aryl, n is 0, 1, 2 or 3, and with their pharmaceutically acceptable acid addition salts for the manufacture of medicaments for the treatment of cognitive enhance or for the treatment of cognitive disorders, anxiety or schizophrenia. The most preferred indication is Alzheimer's disease.

WO 2006/040038 A1

Description

The present invention is concerned with the use of substituted imidazo[1,5-a]triazolo[1,5-d][1,4]benzodiazepine derivatives of the following formula



I

wherein

R^1 is halogen, C_{1-7}-alkyl, C_{2-7}-alkynyl, cycloalkyl, C_{1-7}-alkoxy, OCF_3, -NHR, -NHC(O)R or $-NHSO_2R$;

R^2 is hydrogen, methyl or aryl, which is unsubstituted or substituted by one or two substituents, selected from the group consisting of halogen or C_{1-7}-alkoxy;

R^3 is hydrogen, C_{1-7}-alkyl, C_{2-7}-alkenyl, cycloalkyl, C_{1-7}-alkoxy, $-O(CH_2)_{n+1}$-C_{1-7}alkyl, $-(CH_2)_n$-aryl, which is optionally substituted by C_{1-7}-alkyl or halogen, heteroaryl, -NHR, $-NR_2$, wherein R_2 may be the same or different, or is $-NHCH_2C{=}CH$, or pyrrolidin-1-one;

R is hydrogen, C_{1-7}-alkyl, C_{1-7}-alkyl substituted by halogen, heteroaryl, $-(CH_2)_nO$-C_{1-7}-alkyl, -NH-C_{1-7}-alkyl, cycloalkyl or aryl,

n is 0, 1, 2 or 3;

and with their pharmaceutically acceptable acid addition salts for the manufacture of medicaments for use as cognitive enhancers for use or for the treatment of cognitive disorders, anxiety or schizophrenia. The most preferred indication is Alzheimer's disease.

Compounds of formula I, wherein R^3 is lower alkoxy or hydrogen, have been described in EP 0 519 307 as intermediates for the preparation of tetracyclic imidazodiazepines having an aromatic heterocyclic substitution in the R^3 position for the

treatment of diseases, related to the benzodiazepine receptor, such as epilepsy, anxiety, sleep disorders, symptoms of schizophrenia or senile dementia.

Now it has been found that this class of compounds of formula I show high affinity and selectivity for GABA A α5 receptor binding sites and might be useful as cognitive enhancer or for the treatment of cognitive disorders like Alzheimer's disease.

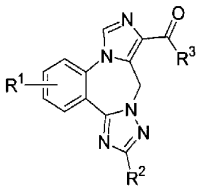
Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) GABA A receptors, which are members of the ligand-gated ion channel superfamily and (2) GABA B receptors, which are members of the G-protein linked receptor family. The GABA A receptor complex which is a membrane-bound heteropentameric protein polymer is composed principally of α, β and γ subunits.

Presently a total number of 21 subunits of the GABA A receptor have been cloned and sequenced. Three types of subunits (α, β and γ) are required for the construction of recombinant GABA A receptors which most closely mimic the biochemical, electrophysiological and pharmacological functions of native GABA A receptors obtained from mammalian brain cells. There is strong evidence that the benzodiazepine binding site lies between the α and γ subunits. Among the recombinant GABA A receptors, α1β2γ2 mimics many effects of the classical type-I BzR subtypes, whereas α2β2γ2, α3β2γ2 and α5β2γ2 ion channels are termed type-II BzR.

It has been shown by McNamara and Skelton in *Psychobiology, 21:101-108* that the benzodiazepine receptor inverse agonist β-CCM enhance spatial learning in the Morris watermaze. However, β-CCM and other conventional benzodiazepine receptor inverse agonists are proconvulsant or convulsant which prevents their use as cognition enhancing agents in humans. In addition, these compounds are non-selective within the GABA A receptor subunits, whereas a GABA A α5 receptor partial or full inverse agonist which is relatively free of activity at GABA A α1 and/or α2 and/or α3 receptor binding sites can be used to provide a medicament which is useful for enhancing cognition with reduced or without proconvulsant activity. It is also possible to use GABA A α5 inverse agonists which are not free of activity at GABA A α1 and/or α2 and/or α3 receptor binding sites but which are functionally selective for α5 containing subunits. However, inverse agonists which are selective for GABA A α5 subunits and are relatively free of activity at GABA A α1, α2 and α3 receptor binding sites are preferred.

Objects of the present invention are the use of compounds of formula I and pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases, which relate to GABA A ligands, new compounds of formula I-A, the preparation of the abovementioned compounds and medicaments containing them.

Furthermore, the invention relates to novel compounds (formula I-A) which are encompassed by formula I as follows:



I-A

wherein

R^1 is halogen, C_{1-7}-alkyl, C_{2-7}-alkynyl, cycloalkyl, C_{1-7}-alkoxy, OCF_3, -NHR, -NHC(O)R or $-NHSO_2R$;

R^2 is hydrogen, methyl or aryl, which is unsubstituted or substituted by one or two substituents, selected from the group consisting of halogen or C_{1-7}-alkoxy;

R^3 is C_{1-7}-alkyl, C_{2-7}-alkenyl, cycloalkyl, $-O(CH_2)_{n+1}-OC_{1-7}$alkyl, $-(CH_2)_n$-aryl, which is optionally substituted by C_{1-7}-alkyl or halogen, heteroaryl, -NHR, $-NR_2$, wherein R_2 may be the same or different, or is $-NHCH_2C{=}CH$, or pyrrolidin-1-one;

R is hydrogen, C_{1-7}-alkyl, C_{1-7}-alkyl substituted by halogen, heteroaryl, $-(CH_2)_nO-C_{1-7}$-alkyl, $-NH-C_{1-7}$-alkyl, cycloalkyl or aryl,

n is 0, 1, 2 or 3;

and to their pharmaceutically acceptable acid addition salts.

Such compounds are

1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-ethanone,

1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,

cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone,

1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-4-phenyl-butan-1-one,

1-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,

cyclopropyl-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,

cyclopropyl-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone,

1-[[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]carbonyl]-2-pyrrolidinone,

3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid prop-2-ynylamide,

3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid benzylamide,

2-methoxy-ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-butan-1-one,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-pentan-1-one,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-but-2(*E*)-en-1-one,

[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-o-tolyl-methanone,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-ethanone,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-3-methyl-butan-1-one,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-2-phenyl-ethanone,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-3-phenyl-propan-1-one,

[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-phenyl-methanone,

[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-thiophen-

2-yl-methanone,
1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-2-(3-chloro-phenyl)-ethanone or
3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid cyclopropyl-amide.

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 "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1-7, preferably from 1 - 4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl or t-butyl.

As used herein, the term "lower alkoxy" denotes a straight- or branched-chain containing from 1-7, preferably from 1 - 4 carbon atoms and wherein the alkyl residue is attached via an oxygen atom.

As used herein, the term "lower alkenyl" denotes a straight- or branched-chain containing from 2-7, preferably from 2 - 4 carbon atoms with at least one double bond.

As used herein, the term "lower alkynyl" denotes a straight- or branched-chain containing from 2-7, preferably from 2 - 4 carbon atoms with at least one triple bond.

As used herein, the term "lower alkyl substituted by halogen" denotes a straight- or branched-chain alkyl group as mentioned above and wherein at least one hydrogen atom is replaced by halogen, for example CF_3, CH_2F, CHF_2, CH_2CF_3.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "cycloalkyl" denotes a cyclic alkyl ring, having from 3 to 7 carbon ring atoms, for example, cyclopropyl, cyclopentyl or cyclohexyl.

The term "aryl" denotes phenyl or naphthyl.

The term "heteroaryl" denotes a five or six membered aromatic ring, wherein at least one carbon atom is replaced by a heteroatom, selected from O, N or S, for example thiophene, imidazole, pyrazole or pyridine.

The term "pharmaceutically acceptable acid addition salts" 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.

Most preferred are compounds, which have a binding activity (Ki) of lower 15 nM and are selective for GABA A α5 subunits and are relatively free of activity at GABA A α1, α2 and α3 receptor binding sites.

Preferred compounds of formula I for the use as described above are those, in which R^3 is C_{1-7}-alkyl, for example the following compounds:
1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-ethanone,
1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,
1-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,
1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,
1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-butan-1-one or
1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-3-methyl-butan-1-one.

Further preferred are compounds for the use as described above, wherein R^3 is cycloalkyl, for example the following compounds:
cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone,
cyclopropyl-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone or
cyclopropyl-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone.

Preferred compounds of formula I for the use as described above are further those, in which R^3 is $-(CH_2)_n$-phenyl, for example the compounds
1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-4-phenyl-butan-1-one or
1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-3-phenyl-propan-1-one.

Preferred compounds of formula I for the use as described above are further those, in which R^3 is alkoxy, for example the compounds
ethyl 3-cyclopropyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-

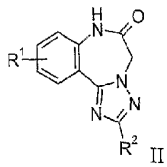
carboxylate,
ethyl 3-methoxy-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,
ethyl 3-acetylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,
ethyl 3-trifluoromethoxy-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,
ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,
ethyl 3-ethynyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,
ethyl 3-(2,2,2-trifluoro-acetylamino)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,
ethyl 3-isobutyrylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,
ethyl 3-(3-methoxy-propionylamino)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,
ethyl 3-formylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,
ethyl 3-ethoxycarbonylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate or
ethyl 3-(3-ethyl-ureido)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate.

Preferred compounds of formula I for the use as described above are further those, in which R^3 is hydrogen, for example the compounds
3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd or
3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd.

Preferred compounds of formula I for the use as described above are further those, in which R^3 is $-NHCH_2C{\equiv}CH$, for example the compound
3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid prop-2-ynylamide.

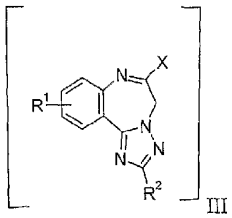
The present compounds of formula I and their pharmaceutically acceptable salts may be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



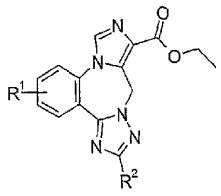
II

with an activating agent, such as phosphorous oxide chloride (for X = Cl) or with diphenylphosphorylchloride (for X = -OP(O)(OPh)$_2$) to a compound of formula



III

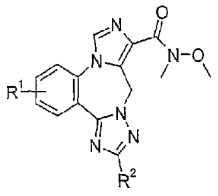
which may be isolated or may be directly reacted with a mixture of lithium diisopropylamide or lithium hexamethyldisilazide and (E)-(dimethylamino-methylamino)-acetic acid ethyl ester or ethylisocyanoacetate to a compound of formula



I-1

wherein R^1 and R^2 have the meaning as described above, or

b) reacting a compound of formula

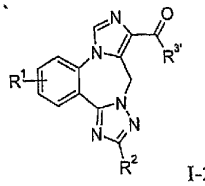


IV

with a compound of formula

$R^{3'}MgX$

to a compound of formula

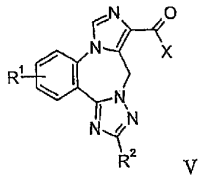


I-2

wherein $R^{3'}$ is C_{1-7}-alkyl, C_{2-7}-alkenyl, cycloalkyl, $-(CH_2)_n$-aryl, optionally substituted by C_{1-7}-alkyl or halogen, heteroaryl, and R^1 and R^2 are as described above

or

c) reacting a compound of formula

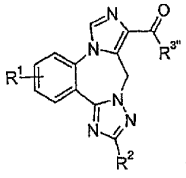


V

with a compound of formulas

NH_2R, NHR_2, wherein R_2 may be the same or different, $NH_2CH_2C{\equiv}CH$, pyrrolidin-1-one or $HO(CH_2)_{n+1}$-O-C_{1-7}-alkyl,

to a compound of formula

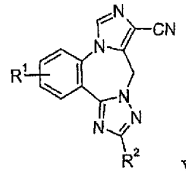


I-3

wherein $R^{3''}$ is -NHR, $-NR_2$, wherein R_2 may be the same or different, or is $-NHCH_2C{\equiv}CH$, pyrrolidin-1-one or $-O(CH_2)_{n+1}$-O-C_{1-7}-alkyl; and R^1 and R^2 are as described above,

or

d) reacting a compound of formula

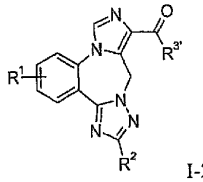


VI

with a compound of formula

$R^{3'}MgX$

to a compound of formula

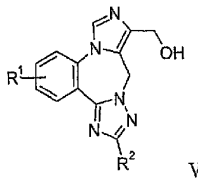


I-2

wherein $R^{3'}$ is C_{1-7}-alkyl, C_{2-7}-alkenyl, cycloalkyl, $(CH_2)_n$-aryl, optionally substituted by C_{1-7}-alkyl or halogen, heteroaryl, and R^1 and R^2 are as described above,

or

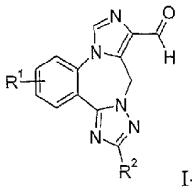
e) reacting a compound of formula



VII

with manganese(IV) oxide

to an aldehyde of formula

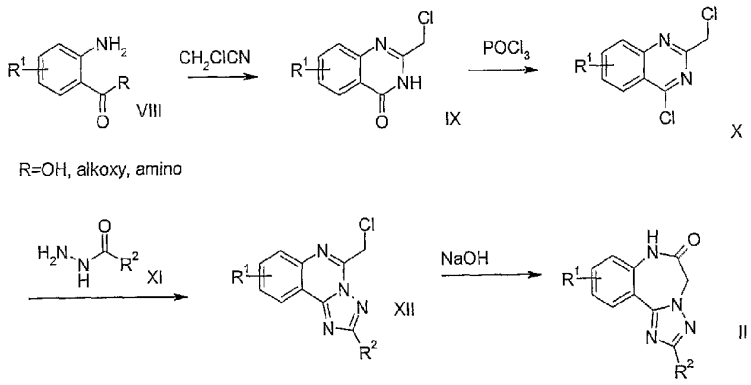


I-4

wherein R^1 and R^2 are as described above,
and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

The following schemes (scheme 1 - 8) describe the processes for preparation of compounds of formula I in more detail. The starting materials are known compounds or may be prepared according to methods known in the art.

Scheme 1

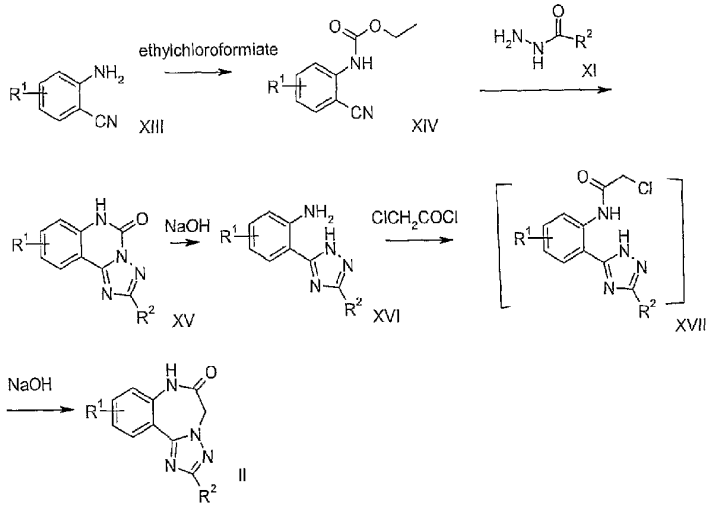


In accordance with scheme 1, a corresponding intermediate compound of formula XIII is known[1] and may be prepared by methods, known in the art, for example in the following way.

A corresponding compound of formula VIII, a R^1-substituted 2-aminobenzoic acid derivative and chloroacetonitrile is dissolved in dioxane and a weak stream of dry HCl is introduced at 5 °C to 15 °C for a period of several hours. After addition of further chloroacetonitrile the mixture is stirred at ambient temperature for several hours. The obtained compound of formula IX is purified in conventional manner and dissolved in chloroform in the presence of N,N-dimethyl-p-toluidine. Phosphorous oxide chloride is added and the solution heated. The obtained compound of formula X is purified by

known methods and heated with a compound of formula XI, a acylhydrazide, in toluene for several hours affording a compound of formula XII, for example the compound 5-chloromethyl -9-fluoro-1,2,4-triazolo[4,3-c]quinazoline. Finally, a compound of II is obtained by dissolving a compound of formula XII in dioxane and treatment with aqueous sodium hydroxide in such manner that the reaction temperature is between 10 °C to 15 °C. Conventional workup and purification affords a corresponding intermediate of formula II, for example 10-fluoro-5H-[1,2,4]triazolo[1,5-d][1,4]benzodiazepin-6(7H)-one.

Scheme 2

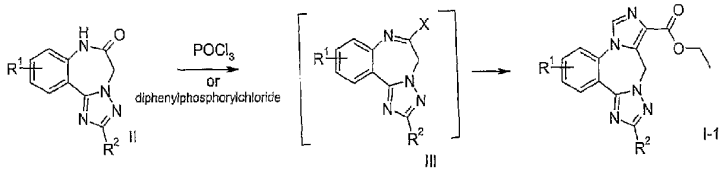


In accordance with scheme 2, a corresponding intermediate compound of formula II may be prepared alternatively in the following way:

A corresponding compound of formula XIII, a R^1-substituted 2-aminobenzonitrile is heated with ethyl chloroformate to obtain a carbamic acid ester of formula XIV, which is treated with a compound of formula XI, an azylhydrazide, in 1-methyl-2-pyrrolidone at 160 °C under removal of ethanol. Conventional workup provides a urea of formula XV which is heated with aqueous sodium hydroxide in ethylenglycol to obtain a compound of formula XVI. Treatment of a compound of formula XVI with chloroacetyl chloride in acetic acid provides an amide of formula XVII, which is treated with aqueous sodium hydroxide in dioxane at ambient temperature to obtain the intermediate of formula II. Alternatively, a compound of formula XVI can be directly transformed to a compound of

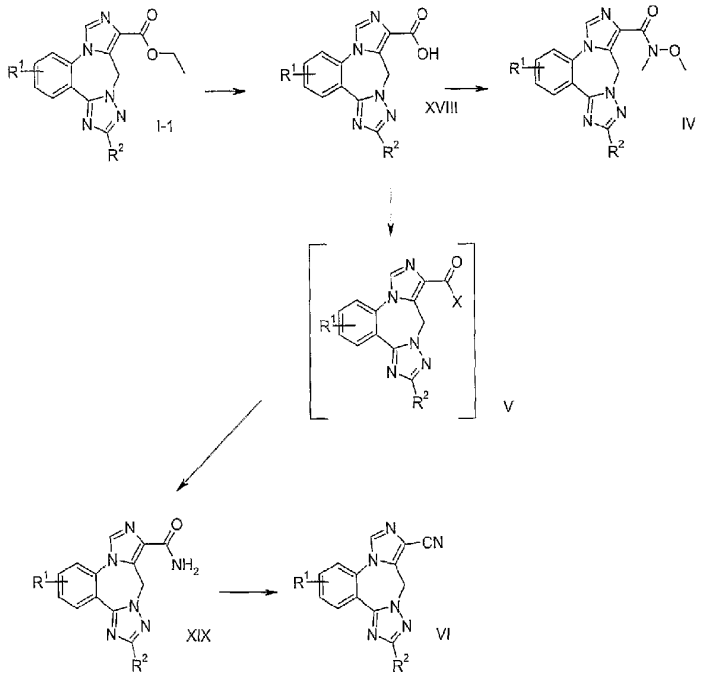
formula II by dissolving a compound of formula XVI in dioxane and pyridine and adding dropwise chloroacetyl chloride at a temperature between 10 °C to 15 °C. After stirring for a short period of time aqueous sodium hydroxide is added and the reaction mixture stirred for several hours at ambient temperature to obtain the compound of formula II.

Scheme 3



In accordance with scheme 3, a compound of formula II is treated with an activation agent in the presence of base at elevated temperature, for example phosphorous oxide chloride in toluene or chloroform in the presence of N,N-dimethyl-p-toluidine, to obtain a compound of formula III which is isolated in conventional manner or directly used in the next reaction step. Finally, a compound of formula I-1 is obtained by the reaction of III with a mixture of a cooled solution of lithium diisopropylamide or lithium hexamethyldisilazide in THF and (E)-(dimethylamino-methylenamino)-acetic acid ethyl ester or with a mixture of a cooled solution of ethyl isocyanoacetate in THF and potassium tert-butoxide or sodium hydride.

Scheme 4

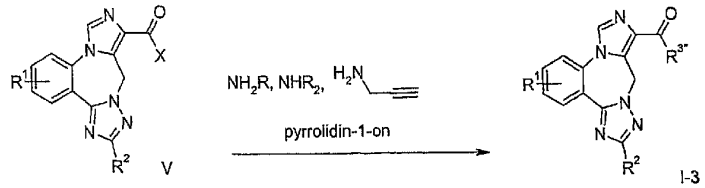


wherein X is halogen and the other definitions are as described above.

According to scheme 4, an carboxylic ester of formula I-1 is saponified to a corresponding carboxylic acid of formula XVIII, which can be treated with an activation reagent, for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, in the presence of *N,O*-dimethylhydroxylamine hydrochloride and a base, for example *N*-methylmorpholine, in a solvent mixture of dichloromethane and DMF at ambient temperature to afford a compound of formula IV. Furthermore, the activation of a carboxylic acid of formula XVIII followed by treatment with ammoniumhydroxide to obtain the carboxylic amide of formula XIX. Reaction of XIX with suitable reagents, for example pyridine and trifluoroacetic anhydride, in an appropriate solvent, for example dioxane or the like, leads to the corresponding cyano-compounds of formula VI, and in accordance with scheme 7, compounds of formula VI can be treated with an appropriate Grignard reagent, for example methylmagnesium chloride, in a suitable solvent, for

example THF or the like, at ambient or elevated temperature affording ketones of the general formula I-2

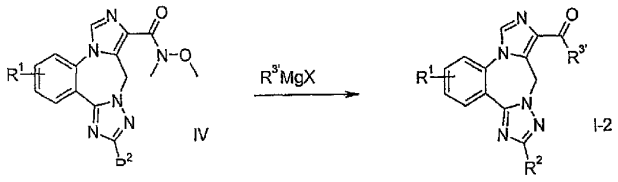
Scheme 5



wherein X is halogen and $R^{3''}$ is -NHR, $-NR_2$, wherein R_2 may be the same or different, or is $-NHCH_2C\equiv CH$, or pyrrolidin-1-one, and R and R^1 and R^2 are as described above.

Amides of the general formula I-3 can be obtained by activation of a carboxylic acid of formula II followed by reaction with an amine, for example benzylamine, in a suitable solvent, for example DMF or the like at ambient or elevated temperature.

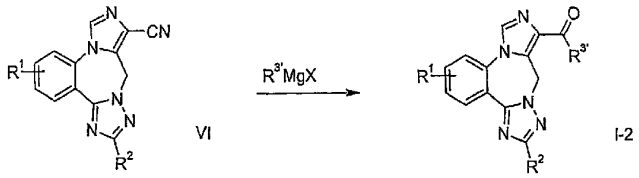
Scheme 6



wherein R^1 and R^2 are as described above and $R^{3'}$ is C_{1-7}-alkyl, cycloalkyl, $-(CH_2)_n$-aryl, optionally substituted by C_{1-7}-alkyl or halogen, heteroaryl, and R^1 and R^2 are as described above.

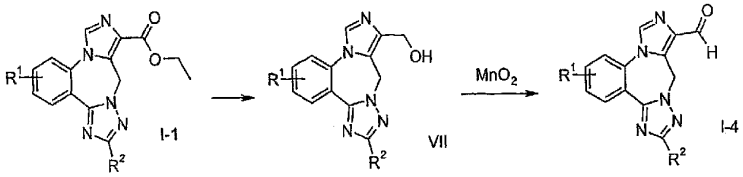
An amide of formula IV can be transformed in a corresponding ketone of general formula I-2 by reaction with an appropriate Grignard reagent, for example methylmagnesium chloride, in a suitable solvent, for example THF or the like, at ambient or elevated temperature.

Scheme 7



wherein R^1 and R^2 are as described above and $R^{3'}$ is C_{1-7}-alkyl , cycloalkyl, -$(CH_2)_n$-aryl, optionally substituted by C_{1-7}-alkyl or halogen, heteroaryl, and R^1 and R^2 are as described above,

Scheme 8



According to scheme 8, a compound of formula I-1 is heated with a reducing agent, for example lithiumborohydride or the like, in a suitable solvent, for example tetrahydrofuran or the like, to obtain an alcohol of formula VII which is oxidized by treatment with manganese(IV) oxide in dichloromethane at ambient temperature to obtain an aldehyde of general formula I-4.

As mentioned earlier, the compounds of formula I and their pharmaceutically usable salts possess valuable pharmacological properties. It has been found that the compounds of the present invention are ligands for GABA A receptors containing the α5 subunit and are therefore useful in the therapy where cognition enhancement is required.

The compounds were investigated in accordance with the test given hereinafter.

Membrane preparation and binding assay

The affinity of compounds at GABA A receptor subtypes was measured by competition for [^{3}H]flumazenil (85 Ci/mmol; Roche) binding to HEK293 cells expressing rat (stably

transfected) or human (transiently transfected) receptors of composition α1β3γ2, α2β3γ2, α3β3γ2 and α5β3γ2.

Cell pellets were suspended in Krebs-tris buffer (4.8 mM KCl, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 120 mM NaCl, 15 mM Tris; pH 7.5; binding assay buffer), homogenized by polytron for ca. 20 sec on ice and centrifuged for 60 min at 4 °C (50000 g; Sorvall, rotor: SM24 = 20000 rpm). The cell pellets were resuspended in Krebs-tris buffer and homogenized by polytron for ca. 15 sec on ice. Protein was measured (Bradford method, Bio-Rad) and aliquots of 1 mL were prepared and stored at –80 °C.

Radioligand binding assays were carried out in a volume of 200 µL (96-well plates) which contained 100 µL of cell memebranes, [^{3}H]flumazenil at a concentration of 1 nM for α1, α2, α3 subunits and 0.5 nM for α5 subunits and the test compound in the range of 10^{-10} – 3 x 10^{-6} M. Nonspecific binding was defined by 10^{-5} M diazepam and typically represented less than 5 % of the total binding. Assays were incubated to equilibrium for 1 hour at 4 °C and harvested onto GF/C uni-filters (Packard) by filtration using a Packard harvester and washing with ice-cold wash buffer (50 mM Tris; pH 7.5). After drying, filter-retained radioactivity was detected by liquid scintillation counting. Ki values were calculated using Excel-Fit (Microsoft) and are the means of two determinations.

The compounds of the accompanying examples were tested in the above described assay, and all were found to possess a Ki value for displacement of [^{3}H]flumazenil from α5 subunits of the rat GABA A receptor of 100 nM or less. In a preferred embodiment the compounds of the invention are binding selective for the α5 subunit relative to the α1, α2 and α3 subunit.

In the table below it is shown the activity data of some preferred compounds:

Example No.	Ki[nM] hα1	Ki[nM] hα2	Ki[nM] hα3	Ki[nM] hα5
1	313.9	183.1	232.7	104.1
2	6.2	3.4	3.9	2.2
3	2.8	2.0	1.8	1.2

4	45.6	60.0	55.9	16.4
5	32.2	28.1	22.4	2.7
6	14.5	18.0	19.9	2.2
9	12.3	12.3	9.0	5.8
10	242.1	67.8	64.9	67.8
12	1.7	0.9	0.7	0.6
14	0.9	1.7	0.9	0.2
19	3.4	1.1	1.4	0.7
21	223.4	134.1	71.9	5.9
23	1.9	3.8	1.8	0.3
24	10.6	4.4	6.4	0.6
25	20.3	28.5	18.8	1.4
26	85.1	106.4	72.7	3.5
31	243.2	260.8	172.6	8.3
33	108.6	159.8	132.7	3.8
38	3.1	7.3	5.7	1.2
39	11.4	73.5	39.7	6.4
41	9.7	24.8	17.7	5.1
42	6.5	8.6	4.9	2.0
43	5.3	22.0	14.4	2.6
44	20.3	26.0	12.4	6.9

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 and vegetable oils.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols.

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. All temperatures are given in degrees Celsius.

Example A

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

	mg/tablet
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:

	mg/capsule
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

Suppositories of the following composition are manufactured:

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

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.

The following examples are provided for illustration of the invention.

Example 1

1-[3-Fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-ethanone

To a solution of 10-cyano-3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine[1] (2.07 g, 7.78 mmol) in THF (100 mL) was added at ambient temperature methylmagnesium bromide (3 N in Et_2O, 39.0 mL, 13.0 mmol) over a period of 5 min. The resulting clear brown solution was stirred for another 2 h. The mixture was carefully poured into aq. HCl (1 N, 200 mL) and extracted with ethyl acetate (3x 200 mL). The combined organic layers were washed with water (250 mL) and brine (250 mL), dried over sodium sulfate and concentrated. Purification of the residue by chromatography (SiO_2, heptane:ethyl acetate:methanol ≈ 20:80:0 to 0:90:10) afforded the title compound (303 mg, 14%) as a white solid. MS: m/e = 282.4 ($M-H^-$).

Example 2

1-[3-Fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one

a) 3-Fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide

A mixture of 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid (20.74 g, 72.7 mmol), *N,O*-dimethylhydroxylamine hydrochloride (11.35 g, 116.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (16.72 g, 87.24 mmol), *N*-methylmorpholine (12.78 mL, 116.3 mmol) and *N,N*-dimethylaminopyridine (300 mg, 3.23 mmol) in a mixture of THF (200 mL) and DMF (40 mL) was stirred at ambient temperature for 18 h. The dichloromethane was distilled off and ice cold water (200 mL) was added. The resulting suspension was stirred for 15 min, filtered and washed with water (100 mL). Drying afforded the title compound (11.46 g, 48%) as white solid. MS: m/e = 329.1 ($M+H^+$).

b) 1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one

To a solution of 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (500 mg, 1.52 mmol) in THF (20 mL) was added at 7-70 °C ethyl magnesium bromide (3M in THF, 1.52 mL, 4.57 mmol). The dry ice bath was removed and the reaction mixture was stirred for 2 h. After cooling to -70 °C further ethyl magnesium bromide (3M in THF, 1.52 mL, 4.57 mmol) was added and the mixture stirred for another 2 h at ambient temperature. The mixture was cooled to 0 °C and aqueous HCl (1 N, 10 mL) was added dropwise. It was diluted with ethyl acetate (20 mL) and aqueous Na_2CO_3 (sat.). The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with aqueous Na_2CO_3 (sat.). Drying over sodium sulfate and purification of the residue by chromatography (SiO_2, heptane:ethyl acetate:dichloromethane = 60:20:20 to 30:50:20:) afforded the title compound (200 mg, 44%) as a white solid. MS: m/e = 298.2 ($M+H^+$).

Example 3

Cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone

a) 3-Fluoro-10-hydroxymethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine

To a suspension of ethyl 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate[1] (9.24 g, 29.5 mmol) in THF (300 mL) was added lithium borohydride (811 mg, 35.4 mmol) and the reaction mixture was heated to reflux for 8 hrs. After cooling to ambient temperature, it was acidified to pH=2 by adding aqueous HCl (1 N). The solvent was evaporated and the residue was taken in aq. NH_4OH (conc., 100 mL). The resulting solid were filtered off, washed with water (3x 10 mL) and

dried (60 °C, vacuo) affording the title compound (6.53 g, 83%) as a white solid. MS: m/e = 272.2 ($M+H^+$).

b) 3-Fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd

To a suspension of 3-fluoro-10-hydroxymethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine (6.00 g, 22.1 mmol) in dichloromethane (200 mL) at 0 °C was added sodium bicarbonate (5.58 g, 66.4 mmol) and Dess-Martin periodinane (14.5 g, 33.2 mmol). After stirring at this temperature for 35 min it was allowed to warm to ambient temperature and stirred for another 1.5 h. Heptane (300 mL) and dichloromethane (100 mL) were added and the orange suspension was stirred for additional 2 h. After filtration through Hyflo® it was carefully washed with dichloromethane and evaporated. Purification of the residue by chromatography (SiO_2, ethyl acetate: methanol = 19:1) afforded the title compound (5.12 g, 86% and dried in vacuo affording the title compound (208 mg, 35%) as an off-white solid. MS: m/e = 270.3 ($M+H^+$).

c) Cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanol

To a freshly prepared cyclopropylmagnesium bromide solution (0.91 M in THF, 35 mL, 31.9 mmol) was added dropwise at 35°C a solution of 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyde (3.00 g, 11.14 mmol) in THF (90 mL). The reaction mixture was stirred for 6 h at 40 °C and 10 h at ambient temperature. Aqueous NH_4Cl (10%, 2 mL) was added and stirring was continued for 15 min. The resulting suspension was concentrated and the residue suspended in a mixture of water and dichloromethane, filtered over Dicalit and the solid was washed with water and dichloromethane. The organic layer was washed with aqueous sodium chloride (sat.) and dried over sodium sulfate. Purification of the residue by chromatography (SiO_2, dichloromethane:methanol =9:1) afforded the title compound (1.60 g, 46%) as a white crystalline solid. MS: m/e = 312.1 $(M+H)^+$.

d) Cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone

To a solution of cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzo-diazepin-10-yl]-methanol (500 mg, 1.61 mmol) in dichloromethane (100 mL) was added manganese(IV) oxide (5.00g, 57.5 mmol) The reaction mixture was stirred for 3 h at ambient temperature before filtered over Dicalit, washed with dichloromethane and dried over magnesium sulfate. Recrystallisation of the residue from

ethyl acetate afforded the title compound (200 mg, 40%) as a white crystalline solid. MS: m/e = 310.2 $(M+H)^+$.

Example 4

1-[3-Fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-4-phenyl-butan-1-one

As described for example 3c) 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzo-diazepine-10-carbaldehyd (1.50 g, 5.57 mmol), using freshly prepared 3-phenyl-propylmagnesium bromide solution (0.68 M in THF, 25 mL, 17.1 mmol) instead of cyclopropylmagnesium bromide solution, was converted to 1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-4-phenyl-butan-1-ol (500 g, 23%) which was obtained as a light yellow foam and directly used in the next reaction step.

As described for example 3d) Cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-4-phenyl-butan-1-ol (800 mg, 2.05 mmol) instead of cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzo-diazepin-10-yl]-methanol was converted to the title compound (400 g, 50%) which was obtained as a white crystalline solid. MS: m/e = 388.1 $[M+H^+]$.

Example 5

1-[3-Chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one

a) 1-[3-Chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-ol

As described for example 3c) 3-Chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd (2.00 g, 7.00 mmol) instead of 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzo-diazepine-10-carbaldehyd, using freshly prepared ethylmagnesium bromide solution (1.05 M in THF, 20 mL, 21.0 mmol) instead of cyclopropylmagnesium bromide solution, was converted to the title compound (1.30 g, 59%) which was obtained as a light yellow foam. MS: m/e = 316.0 $[M+H^+]$.

b) 1-[3-Chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one

As described for example 3d) 1-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-ol (1.30 g, 4.12 mmol) instead of cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzo-diazepin-10-yl]-methanol was converted to the title compound (1.05 g, 81%) which was obtained as an off-white

crystalline solid. MS: m/e = 314.1 $[M+H^+]$.

Example 6

Cyclopropyl-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone

a) Cyclopropyl-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanol

As described for example 3c) 3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd (3.50 g, 12.3 mmol) instead of 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzo-diazepine-10-carbaldehyd was converted to the title compound (2.70 g, 67%) which was obtained as a white crystalline solid. MS: m/e = 328.0 $[M+H^+]$.

b) Cyclopropyl-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone

As described for example 3d) cyclopropyl-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanol (2.00 g, 6.10 mmol) instead of cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzo-diazepin-10-yl]-methanol was converted to the title compound (1.50 g, 76%) which was obtained as a white crystalline solid. MS: m/e = 326.1 $[M+H^+]$.

Example 7

1-[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one

a) 3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid

A mixture of ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (cp. example 21) (7.08 g, 18.9 mmol), NaOH 1N (76 ml, 76 mmol) in ethanol (70 mL) was stirred for 18 h at ambient temperature. The solvent was distilled off (55 mbar, 45°C) and the resulting light brown suspension was adjusted with aqueous HCl (1 N, 85 mL) to pH=1.5 at 0 °C. The suspension was stirred for 1 h at 0 °C, filtered off and washed twice with water (total 50 mL). The solid was dried in vacuo at 60 °C affording the title compound (6.65 g, 99%) as a light brown solid. MS: m/e = 346.0/348.2 $[M+H]^+$.

b) 3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide

To a mixture of 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid (4.9 g, 14.2 mmol), *N,O*-dimethylhydroxylamine hydrochloride (2.21 g, 22.7 mmol), *N*-methylmorpholine (2.3 mL, 22 mmol) and 4-dimethylaminopyridine (170 mg, 1.4 mmol) in dichloromethane (100 mL) and DMF (10 mL) was added at 0 °C 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.26 g, 17.0 mmol). The reaction mixture was stirred for 18 h at ambient temperature. The dichloromethane was distilled off and ice-cold water (100 mL) was added to the residue. The resulting suspension was stirred for 15 min, filtered and washed with water (50 mL). The solid was dried in vacuo affording the title compound (5.06 g, 92%) as an off-white solid. MS: m/e = 389.0/391.0 $[M+H]^+$.

c) 1-[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one

To a suspension of 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (500 mg, 1.29 mmol) in THF (20 mL) was added ethylmagnesium bromide solution (3 M in THF, 2.6 mL, 7.8 mmol) at -70 °C under a nitrogen atmosphere. The reaction mixture was stirred in a thawing dry ice bath for 3 h. It was cooled to 0 °C and aqueous HCl (1 N, 15 mL) was added dropwise. The resulting mixture was stirred for 5 min at ambient temperature before diluted with dichloromethane (20 mL) and aqueous Na_2CO_3 (sat., 20 mL). The aqueous layer was extracted with dichloromethane (20 mL) and the combined organic layers were dried over sodium sulfate. Purification of the residue by chromatography (SiO_2, heptane:ethyl acetate:dichloromethane = 60:20:20 to 30:50:20:) afforded the title compound (91 mg, 20%) as a white solid. MS: m/e = 358.1/360.0 $(M+H)^+$.

Example 8

Cyclopropyl-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone

As described for example 7c) 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (500 mg, 1.29 mmol), using cyclopropylmagnesium bromide solution (0.5 M in THF, 7.7 mL, 3.85 mmol) instead of ethylmagnesium bromide solution, was converted to the title compound (294 mg, 62%) which was obtained as a white solid. MS: m/e = 370.0/372.1 $[M+H]^+$.

Example 9

1-[[3-Fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]carbonyl]-2-pyrrolidinone

A mixture of 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid (2.00 g, 7.01 mmol) and thionyl chloride (1.53 mL, 21.0 mmol) in benzene (20 mL) was stirred for 2 h at reflux. Further thionyl chloride (1.50 mL, 20.6 mmol) was added and stirring was continued for another 2 h at this temperature. The resulting clear solution was concentrated, the residue dissolved in THF (60 mL) and added dropwise to a solution of *N*-trimethylsilyl-pyrrolidin-2-one (1.13 g, 7.18 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred for 1 h at ambient temperature and for 1.5 h at 70 °C. The solvent was distilled off and the residue dissolved in dichloromethane, washed with aqueous $NaHCO_3$ (sat.) and water and was dried over odium sulfate. Recrystallisation from methanol afforded the title compound (600 mg, 24%) as a white crystalline solid. MS: m/e = 353.1 $(M+H)^+$.

Example 10

3-Fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid prop-2-ynylamide

To suspension of 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid (500 mg, 1.75 mmol) in DMF (10 mL) was added 1,1'-carbonyl-diimidazole (426 mg, 2.63 mmol). The reaction mixture was stirred for 6 h at 80 °C. After cooling to ambient temperature propargylamine (300 µL, 4.38 mmol) was added and stirring was continued for 16 h at this temperature. The mixture was diluted with water (30 mL) and saturated aqueous $NaHCO_3$ (10 mL) and was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate. Recrystallisation from ethyl acetate afforded the title compound (72 mg, 0.22 mmol) as a white solid. MS: m/e = 323.3 $[M+H^+]$.

Example 11

3-Fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid benzylamide

As described for example 10, 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzo-diazepine-10-carboxylic acid (500 mg, 1.75 mmol), using benzylamine instead of propargylamine, was converted to the title compound (540 mg, 82%) which was obtained as an white solid. MS: m/e = 375.3 $[M+H^+]$.

Example 12

Ethyl 3-cyclopropyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

A suspension of ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (example 23) (200 mg, 0.53 mmol) in THF (10 mL) was heated to 65°C. To the resulting solution were added tetrakis(triphenylphosphine)palladium(0) (31 mg, 0.03 mmol) and cyclopropylzinc bromide solution (0.38 M in THF, 3.5 mL, 1.3 mmol) and the reaction mixture was stirred for 1 h at 65 °C. It was diluted with water (5 mL) and acidified to pH=1 with aqueous HCl (1 N). The THF was distilled off, toluene (5 mL) was added and the mixture stirred for 30 min at ambient temperature before filtered and washed with water. Purification of the residue by chromatography (SiO_2, heptane:ethyl acetate:dichloromethane = 60:20:20 to 30:50:20:) afforded the title compound (61 mg, 37%) as a white solid. MS: m/e = 336.3 $(M+H)^+$.

Example 13

Ethyl 3-bromo-6-methyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

a) 3-Bromo-2-methyl-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one
As described for example 23b) 4-bromo-2-cyano-phenyl)-carbamic acid ethyl ester (30.0 g, 111 mmol), using acetic acid hydrazide instead of formylhydrazine, was converted to the title compound (28.5 g, 91%) which was obtained as an off-white solid. MS: m/e = 277.0/279.1 $[M-H]^-$.

b) 4-Bromo-2-(5-methyl-2H-[1,2,4]triazol-3-yl)-phenylamine
As described for example 23c) 9-bromo-2-methyl-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one (28.5 g, 102 mmol), instead of 9-bromo-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one, was converted to the title compound (25.5 g, 99%) which was obtained as an off-white solid. MS: m/e = 251.0/253.1 $[M-H]^-$.

c) 9-Bromo-2-methyl-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one
As described for example 23d) 4-bromo-2-(5-methyl-2H-[1,2,4]triazol-3-yl)-phenylamine (24.9 g, 98.3 mmol), instead of 4-bromo-2-(2H-[1,2,4]triazol-3-yl)-phenylamine, was converted to the title compound (17.0 g, 59%) which was obtained as an off-white solid. MS: m/e = 291.0/293.2 $[M-H]^-$.

d) Ethyl 3-bromo-6-methyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate
As described for example 23e) 9-bromo-2-methyl-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one (16.8 g, 57.3 mmol) instead of 9-bromo-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-

one was converted to the title compound (14.7 g, 66%) which was obtained as an off-white solid. MS: m/e = 388.2/390.1 $[M+H]^+$.

Example 14

Ethyl 3-methoxy-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

a) 3-Methoxy-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid

To a solution of ethyl 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (200 mg, 0.64 mmol) in DMSO (2 mL) was added sodium methoxide (103 mg, 1.92 mmol). The reaction mixture was stirred for 18 h at 60 °C and 24 h at 150 °C. Further sodium methoxide (103 mg, 1.92 mmol) was added and stirring was continued for another 24 h at 150 °C. The mixture was poured onto ice (30 g), was saturated with sodium chloride and was extracted with ethyl acetate. The combined organic layers were washed with brine. Drying over sodium sulfate afforded the title compound (100 mg, 53%) as a light brown solid. MS: m/e = 296.3 $[M+H]^+$.

b) Ethyl 3-methoxy-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

To s auspension of 3-methoxy-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid (81 mg, 0.27 mmol) in ethanol (10 mL) was added sulfuric acid (73 □L, 1.36 mmol) and the mixture was stirred for 48 h at 80 °C under a nitrogen atmosphere. It was concentrated, aqueous Na_2CO_3 (sat., 10 mL) added and extracted with ethyl acetate. It was dried over sodium sulfate and concentrated. The residue was dissolved in ethyl acetate (5 mL) and heptane (5 mL) was added. The resulting solid was filtered. Recrystallisation from ethyl acetate:heptane (1:1) afforded the title compound (21 mg, 24%) as a white solid. MS: m/e = 326.2 $[M+H]^+$.

Example 15

Ethyl 3-chloro-6-methyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

a) 4-Chloro-2-cyano-phenyl)-carbamic acid ethyl ester

As described for example 23a) 2-amino-5-chlorobenzonitrile (33.4 g, 219 mmol), instead of 2-amino-5-bromobenzonitrile, was converted to the title compound (46.9 g, 95%) which was obtained as a light yellow solid. MS: m/e = 242.3 $[M+NH_4]^+$.

b) 9-Chloro-2-methyl-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one

As described for example 23b) 4-chloro-2-cyano-phenyl)-carbamic acid ethyl ester (10.0 g, 44.5 mmol), instead of 4-bromo-2-cyano-phenyl)-carbamic acid ethyl ester, using acetic acid hydrazide instead of formylhydrazine, was converted to the title compound (9.81 g, 94%) which was obtained as a light yellow solid. MS: m/e = 234.9 $[M]^+$.

c) 4-Chloro-2-(5-methyl-2H-[1,2,4]triazol-3-yl)-phenylamine

As described for example 23c) 9-chloro-2-methyl-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one (9.67 g, 41.2 mmol), instead of 9-bromo-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one, was converted to the title compound (6.57 g, 76%) which was obtained as an off-white solid. MS: m/e = 209.0 $[M+H]^+$.

d) 9-Chloro-2-methyl-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one

As described for example 23d) 4-chloro-2-(5-methyl-2H-[1,2,4]triazol-3-yl)-phenylamine (9.44 g, 30.9 mmol), instead of 4-bromo-2-(2H-[1,2,4]triazol-3-yl)-phenylamine, was converted to the title compound (4.83 g, 63%) which was obtained as a white solid. MS: m/e = 248.9 $[M]^+$.

e) Ethyl 3-chloro-6-methyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

As described for example 23e) 9-chloro-2-methyl-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one (2.49 g, 10.0 mmol) instead of 9-bromo-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one was converted to the title compound (1.19 g, 35%) which was obtained as a light brown solid. MS: m/e = 344.0 $[M+H]^+$.

Example 16

Ethyl 3-chloro-6-(4-fluorophenyl)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

a) 9-Chloro-2-(4-fluorophenyl)-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one

As described for example 23b) 4-chloro-2-cyano-phenyl)-carbamic acid ethyl ester (5.00 g, 22.3 mmol), instead of 4-bromo-2-cyano-phenyl)-carbamic acid ethyl ester, using 4-fluorbenzhydrazide instead of formylhydrazine, was converted to the title compound (6.90 g, 98%) which was obtained as a light yellow solid. MS: m/e = 315.1 $[M+H]^+$.

b) 4-Chloro-2-(4-fluorophenyl)-2H-[1,2,4]triazol-3-yl)-phenylamine

As described for example 23c) 9-chloro-2-(4-fluorophenyl)-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one (6.82 g, 21.7 mmol), instead of 9-bromo-6H-[1,2,4]triazolo[1,5-

c]quinazolin-5-one, was converted to the title compound (3.98 g, 64%) which was obtained as a light yellow solid. MS: m/e = 289.0 $[M+H]^+$.

c) 9-Chloro-2-(4-fluorophenyl)-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one
As described for example 23d) 4-chloro-2-(5-(4-fluorophenyl)-2H-[1,2,4]triazol-3-yl)-phenylamine (3.91 g, 13.6 mmol), instead of 4-bromo-2-(2H-[1,2,4]triazol-3-yl)-phenylamine, was converted to the title compound (2.97 g, 67%) which was obtained as an off-white solid. MS: m/e = 329.0 $[M+H]^+$.

d) Ethyl 3-chloro-6-(4-fluorophenyl)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate
As described for example 23e) 9-chloro-2-(4-fluorophenyl)-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one (2.86 g, 8.69 mmol) instead of 9-bromo-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one was converted to the title compound (63 mg, 1.7%) which was obtained as a light yellow solid. MS: m/e = 424.1 $[M+H]^+$.

Example 17

Ethyl 3-chloro-6-(3,4-dimethoxyphenyl)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

a) 9-Chloro-2-(3,4-dimethoxyphenyl)-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one
As described for example 23b) 4-chloro-2-cyano-phenyl)-carbamic acid ethyl ester (5.00 g, 22.3 mmol), instead of 4-bromo-2-cyano-phenyl)-carbamic acid ethyl ester, using 3,4-dimethoxybenzhydrazide instead of formylhydrazine, was converted to the title compound (7.55 g, 95%) which was obtained as a light yellow solid. MS: m/e = 375.4 $[M-H]^-$.

b) 4-Chloro-2-(3,4-dimethoxyphenyl)-2H-[1,2,4]triazol-3-yl)-phenylamine
As described for example 23c) 9-chloro-2-(3,4-dimethoxyphenyl)-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one (7.37 g, 20.7 mmol), instead of 9-bromo-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one, was converted to the title compound (6.24 g, 91%) which was obtained as a light yellow solid. MS: m/e = 331.2 $[M+H]^+$.

c) 9-Chloro-2-(3,4-dimethoxyphenyl)-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one
As described for example 23d) 4-chloro-2-(5-(3,4-dimethoxyphenyl)-2H-[1,2,4]triazol-3-yl)-phenylamine (6.18 g, 18.7 mmol), instead of 4-bromo-2-(2H-[1,2,4]triazol-3-yl)-phenylamine, was converted to the title compound (5.06 g, 73%) which was obtained as an off-white solid. MS: m/e = 371.0 $[M+H]^+$.

d) Ethyl 3-chloro-6-(3,4-dimethoxyphenyl)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

As described for example 23e) 9-chloro-2-(3,4-dimethoxyphenyl)-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one (3.71 g, 10.0 mmol) instead of 9-bromo-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one was converted to the title compound (2.24 g, 48%) which was obtained as a light brown solid. MS: m/e = 466.2 $[M+H]^+$.

Example 18

Ethyl 3-acetylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

a) Ethyl 3-amino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

As described for example 23e) 9-amino-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one (8.60 g, 40.0 mmol), instead of 9-bromo-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one, was converted to the title compound which was obtained as a white solid. MS: m/e = 311.2 $[M+H]^+$.

b) Ethyl 3-acetylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

To a solution of 3-amino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (310 mg, 1.00 mmol) in pyridine (30 mL) was added dropwise at 10 °C acetic anhydride (0.50 mL, 5.29 mmol) and the reaction mixture was stirred at ambient temperature for 24 h. The resulting solid was filtered and washed with toluene. Recrystallisation from ethyl acetate provided the title compound (260 mg, 74%) as a white crystalline solid. MS: m/e = 353.2 $[M+H]^+$.

Example 19

Ethyl 3-trifluoromethoxy-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

a) 2-Amino-5-trifluoromethoxybenzonitrile

To a solution of 2-bromo-4-(trifluoromethoxy)aniline (15.1 g, 60.0 mmol) in *N*-methylpyrrolidone (100 mL) was added copper cyanide (10.6 g, 118 mmol) and the reaction mixture was stirred for 6.5 h at 163 °C. After cooling to ambient temperature it was poured onto ice-water (300 mL) and aqueous ammonia (350 mL). The resulting brown precipitate was collected by filtration, washed with water (150 mL) and dissolved in dichloromethane (350 mL). The insoluble material was removed by filtration and the filtrate was washed with brine (100 mL) and dried over sodium sulfate. Purification by

chromatography (SiO_2, heptane:ethyl acetate = 95:5 to 25:75:) afforded the title compound (9.09 g, 76%) as a brown solid. MS: m/e = 405.1 $[2M+H]^+$.

b) (2-Cyano-4-trifluoromethoxy-phenyl)-carbamic acid ethyl ester

As described for example 23a) 2-amino-5-trifluoromethoxybenzonitrile (8.89 g, 44.0 mmol), instead of 2-amino-5-bromobenzonitrile, was converted to the title compound (8.53 g, 71%) which was obtained as a yellow solid. MS: m/e = 275.2 $[M+H]^+$.

c) 9-Trifluoromethoxy-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one

As described for example 23b) (2-cyano-4-trifluoromethoxy-phenyl)-carbamic acid ethyl ester (8.31 g, 30.3 mmol), instead of (4-bromo-2-cyano-phenyl)-carbamic acid ethyl ester, was converted to the title compound (5.63 g, 69%) which was obtained as a yellow solid. MS: m/e = 271.2 $[M+H]^+$.

d) 4-Trifluoromethoxy-2-(2H-[1,2,4]triazol-3-yl)-phenylamine

As described for example 23c) 9-trifluoromethoxy-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one (5.51 g, 20.4 mmol), instead of 9-bromo-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one, was converted to the title compound (3.22 g, 65%) which was obtained as a light brown solid. MS: m/e = 245.2 $[M+H]^+$.

e) 2-Chloro-N-[2-(2H-[1,2,4]triazol-3-yl)-4-trifluoromethoxy-phenyl]-acetamide

To a cooled solution of 4-trifluoromethoxy-2-(2H-[1,2,4]triazol-3-yl)-phenylamine (3.00 g, 12.3 mmol) in acetic acid (62 mL) was added dropwise chloroacetyl chloride (1.96 mL, 24.6 mmol). The resulting light brown suspension was stirred for 20 h at ambient temperature and was then poured into water (246 mL) and stirred for another 3 h. The precipitate was filtered off and washed with water. Drying in vacuo afforded the title compound (3.22 g, 82%) as an off-white solid. MS: m/e = 323.1 $[M+H]^+$.

f) 9-Trifluoromethoxy-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one

To a solution of 2-chloro-N-[2-(2H-[1,2,4]triazol-3-yl)-4-trifluoromethoxy-phenyl]-acetamide (3.15 g, 9.82 mmol) in dioxane (100 mL) was added aqueous sodium hydroxide (32%, 2.18 mL, 23.6 mmol) and the reaction mixture was stirred for 19 h at ambient temperature. It was poured onto aqueous ammonium chloride (1M, 50 mL) and the organic solvent was removed by destillation. The resulting suspension was filtered and the solid was washed with ice-cold water (50 mL). Drying in vacuo afforded the title compound (682 mg, 24%) as a light yellow solid. MS: m/e = 285.0 $[M+H]^+$.

g) 5-[1,2,4]Triazol-1-yl-9-trifluoromethoxy-4H-1,3,3a,6-tetraaza-benzo[e]azulene

To a solution of 1,2,4-triazole (1.00 g, 14.5 mmol) and N-ethyldiisopropylamine (2.64 mL, 15.4 mmol) in acetonitrile (13 mL) was added dropwise phosphorous oxychloride (0.40 mL, 4.40 mmol) at 0 °C. The solution was stirred for 2 h at 0 °C before 5-[1,2,4]triazol-1-yl-9-trifluoromethoxy-4H-1,3,3a,6-tetraaza-benzo[e]azulene (625 mg, 2.20 mmol) was added and stirring was continued for 20 h at 90 °C. The reaction mixture was cooled to ambient temperature and poured onto ice-water, stirred for 15 min and was filtered off. Washing with water and drying in vacuo afforded the title compound (357 mg, 48%) as a light brown solid. MS: m/e = 336.2 $[M+H]^+$.

h) Ethyl 3-trifluoromethoxy-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

To a solution of potassium tert-butylate (156 mg, 1.39 mmol) in DMF (3.3 mL) was added dropwise ethyl isocyanoacetate (177 mg, 14.9 mmol) over a period of 1 min at -50 °C. The reaction mixture was stirred for 1 h at this temperature before 5-[1,2,4]triazol-1-yl-9-trifluoromethoxy-4H-1,3,3a,6-tetraaza-benzo[e]azulene (333 mg, 1 mmol) was added in one portion. After stirring for 30 min at -50 °C, the reaction mixture was allowed to warm to ambient temperature stirred for 1.5 h. Acetic acid (0.34 mL, 59.6 mmol) was added at 0 °C and the mixture was stirred for another 30 min before poured into ice-water and filtered off and washed with water. Purification by chromatography (SiO_2, heptane:ethyl acetate:dichloromethane = 75:15:10 to 0:90:10) afforded the title compound (72 mg, 19%) as a white solid. MS: m/e = 380.1 $[M+H]^+$.

Example 20

3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd

a) 3-Bromo-10-hydroxymethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine

As described for example 3a, ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (cp. Example 23) (1.03 g, 2.75 mmol), instead of ethyl 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate, was converted to the title compound (652 mg, 71%) which was obtained as a white solid. MS: m/e = 332.1/334.1 ($M+H^+$).

b) 3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd

As described for example 2a, 3-bromo-10-hydroxymethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine (600 mg, 1.81 mmol), instead of 3-chloro-

10-hydroxymethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine, was converted to the title compound (208 mg, 35%) which was obtained as a white solid. MS: m/e = 330.1/332.1 ($M+H^+$).

Example 21

3-Chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd

a) 3-Chloro-10-hydroxymethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine

To a suspension of ethyl 3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate[1] (10.0 g, 30.3 mmol) in THF (400 mL) was added lithium borohydride (800 mg, 34.9 mmol) and the reaction mixture was heated to reflux for 7 hrs. After cooling to ambient temperature, it was acidified to pH=2 by adding aq HCl (1 N) and diluted with water (50 mL). The solvent was evaporated and the residue was taken in aq. NH_4OH (conc., 100 mL). The resulting solid were filtered off, washed with water (3x 10 mL) and dried (60 °C, vacuo) affording the title compound (4.01 g, 45.8%) as a white solid. MS: m/e = 287.9 (M^+).

b) 3-Chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd

To a solution of 3-chloro-10-hydroxymethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine (15.0 g, 52.1 mmol) in dichloromethane (1.5 L) was added manganese(IV) oxide (188 g; 1.94 mol) and the mixture was stirred at ambient temperature for 24 h. It was filtered over dicalite, washed with dichloromethane and concentrated. The residue was dissolved in dichloromethane (700 mL) at 40 °C and ethyl acetate (100 mL) was added. The product started to crystallise. After cooling the dichloromethane was evaporated and the solid filtered. Drying in vacuo afforded the title compound (11.8 g, 79.2%) as a yellow crystalline solid. MS: m/e = 286.1 ($M+H^+$).

Example 22

Ethyl 3-chloro-6-phenyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

a) 9-Chloro-2-phenyl-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one

As described for example 23b) 4-chloro-2-cyano-phenyl)-carbamic acid ethyl ester (5.00 g, 22.3 mmol), instead of 4-bromo-2-cyano-phenyl)-carbamic acid ethyl ester, using benzhydrazide instead of formylhydrazine, was converted to the title compound (6.50 g, 98%) which was obtained as a light yellow solid. MS: m/e = 297.1 $[M+H]^+$.

b) 4-Chloro-2-phenyl-2H-[1,2,4]triazol-3-yl)-phenylamine

As described for example 23c) 9-chloro-2-phenyl-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one (6.34 g, 21.4 mmol), instead of 9-bromo-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one, was converted to the title compound (5.35 g, 92%) which was obtained as a light yellow solid. MS: m/e = 271.0 $[M+H]^+$.

c) 9-Chloro-2-phenyl-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one

As described for example 23d) 4-chloro-2-(5-phenyl-2H-[1,2,4]triazol-3-yl)-phenylamine (5.24 g, 19.3 mmol), instead of 4-bromo-2-(2H-[1,2,4]triazol-3-yl)-phenylamine, was converted to the title compound (4.40 g, 73%) which was obtained as an off-white solid. MS: m/e = 311.0 $[M+H]^+$.

d) Ethyl 3-chloro-6-phenyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

As described for example 23e) 9-chloro-2-phenyl-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one (3.11 g, 10.0 mmol) instead of 9-bromo-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one was converted to the title compound (1.26 g, 31%) which was obtained as a light yellow solid. MS: m/e = 424.1 $[M+NH_4]^+$.

Example 23

Ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

a) 4-Bromo-2-cyano-phenyl)-carbamic acid ethyl ester

A suspension of 2-amino-5-bromobenzonitrile (58.5 g, 297 mmol) in ethyl chloroformate (141 ml, 1.48 mol) was heated at reflux for 5 h. The excess ethyl chloroformate (99 mL) was distilled off and toluene (96 mL) was added. Slow addition of cyclohexane (228 mL) induced crystallization. The resulting solid was collected by filtration and rinsed with cyclohexane. Drying in vacuo afforded the title compound (54.3 g, 68%) as an orange solid. MS: m/e = 267.1/269.2 $[M-H^-]$.

b) 9-Bromo-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one

To a solution of 4-bromo-2-cyano-phenyl)-carbamic acid ethyl ester (40.4 g, 150 mmol) in NMP (170 mL) was added formylhydrazine (10.0 g, 150 mmol). The resulting mixture was stirred for 1.5 h at 160 °C under a gentle nitrogen sweep. It was cooled to below 100 °C and water (340 mL) was added slowly. The resulting slurry was cooled to 25 °C and stirred for 15 min. The solid was collected by filtration and washed with water and 2-propanol. Drying in vacuo afforded the title compound (32.4 g, 81%) as a light yellow solid. MS: m/e = 264.9/267.0 $[M+H^+]$.

c) 4-Bromo-2-(2H-[1,2,4]triazol-3-yl)-phenylamine

To a well stirred slurry of 9-bromo-6H-[1,2,4]triazolo[1,5-c]quinazolin-5-one (32.0 g, 171 mmol) in ethylene glycol (146 mL) which was heated at 100 °C, was added aqueous NaOH (32%, 22.4 ml, 241 mmol). The slurry was heated at 140 °C for 17.5 h. The resulting solution was cooled to 27 °C and the product began to crystallize. Water (146 mL) and 1-octanol (1.73 mL) were added and the pH of the suspension was adjusted to 6.5 by the slow addition of glacial acetic acid (14 mL). The resulting slurry was stirred for 30 min, the solid was collected by filtration and washed with water and 2-propanol. Drying in vacuo afforded the title compound (25.2 g, 87%) as a light yellow solid. MS: m/e = 239.0/241.1 $[M+H^+]$.

d) 9-Bromo-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one

A solution of 4-bromo-2-(2H-[1,2,4]triazol-3-yl)-phenylamine (25.0 g, 105 mmol) in dioxane (870 mL) and pyridine (10.0 mL) was cooled to 12 °C. A solution of chloroacetyl chloride (9.56 ml, 121 mmol) in diethylether (34.7 mL) was added dropwise over a period of 8 min. The mixture was stirred at 10 °C - 12 °C for 75 min and treated within 5 min with aqueous NaOH (2 N, 126 ml, 251 mmol). The mixture was stirred for 17.5 h at ambient temperature. The pH thereby dropped to about pH=9 and it was adjusted to pH=8 with HCl (3 N, 6mL). After evaporation the residue was stirred at 15 °C for 30 min in water (650 mL) and ethyl acetate (22 mL). The crystals were filtered off, washed with cold water and dried in vacuo. Trituration in ethyl acetate (100 mL) afforded the title compound (13.4 g, 46%) as a light yellow solid. MS: m/e = 279.0/281.0 $[M+H]^+$.

e) Ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

To a suspension of 9-bromo-6H-1,3,3a,6-tetraaza-benzo[e]azulen-5-one (10.7 g, 38.5 mmol) in chloroform (270 ml, filtrated over Alox basic) was added *N,N*-dimethyl-*p*-toluidine (13.9 ml, 96.1 mmol) and phosphorous oxychloride (5.28 ml, 57.7 mmol). The mixture was stirred for 22 h at reflux, then cooled to 30 °C and poured into aq $NaHCO_3$ (10%, 575 mL). After extraction with chloroform (50 mL) the organic layers were dried over sodium sulfate and concentrated.

In the meantime potassium tert-butylate (4.31 g, 38. 5mmol) was added in portions to a solution of ethyl isocyanoacetate (4.42 ml, 38.5 mmol) in THF (115 mL) at -25 °C to -10 °C. The resulting suspension was stirred for 45 min at -10 °C and then cooled to -65 °C. The solution from above was added dropwise within 10 min and the mixture was stirred for 16 h at ambient temperature. Acetic acid (1.6 mL) was added, stirred for 15 min and then poured into aq $NaHCO_3$ (5%, 460 mL) and ethyl acetate (96 mL). The resulting

crystals were filtered off, washed with ethyl acetate (25 mL), water (50 mL) and ethyl acetate (25 mL). Drying in vacuo afforded the title compound (4.81 g, 33%) as a light brown solid. MS: m/e = 373.7/375.7 $[M]^+$.

Example 24

Ethyl 3-ethynyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

a) Ethyl 3-trimethylsilanylethynyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

A suspension of ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (Example 23) (374 mg, 1.00 mmol), trimethylsilylacetylene (221 µl, 1.55 mmol), bis(triphenylphosphine)palladium (II) chloride (35 mg, 0.05 mmol), triphenylphosphine (8 mg, 0.03 mmol) and triethylamine (500 µl, 3.60 mmol) in THF (5 ml) was stirred for 15 min at ambient temperature. Then cuprous bromide (1.4 mg, 0.01 mmol) was added and the reaction mixture was stirred for 21 h at 70 °C under an argon atmosphere. It was diluted with ethyl acetate (20 ml) and washed with aqueous citric acid (10%, 40 ml). The aqueous layer was extracted with ethyl acetate (40 ml) and the combined organic layers were dried over sodium sulfate and evaporated. Purification by chromatography (SiO_2, heptane:ethyl acetate:dichloromethane:methanol = 75:15:10:0 to 0:80:10:10) afforded the title compound (245 mg, 63%) as a yellow foam. MS: m/e = 392.2 $[M+H]^+$.

b) Ethyl 3-ethynyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

To a solution of ethyl 3-trimethylsilanylethynyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (196 mg, 0.50 mmol) in THF (1.8ml) and methanol (0.18 ml) was added tetrabutylammonium fluoride trihydrate (166 mg, 0.74 mmol) at -70 °C. After stirring for 30 min at this temperature the dry ice bath was replaced by an ice bath. After additional 1.5 h stirring, the mixture was diluted with ethyl acetate (10 ml) and was washed with aqueous sodium hydrogencarbonate (saturated). The aqueous layers were extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate and evaporated. Purification by chromatography (SiO_2, heptane:ethyl acetate:dichloromethane:methanol = 75:15:10:0 to 0:80:10:10) afforded the title compound (135 mg, 84%) as a white solid. MS: m/e = 320.0 $[M+H]^+$.

Example 25

2-Methoxy-ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

To a mixture of sodium dihydro-bis(2-methoxyethoxy)aluminate (3.5 M in toluene, 0.19 ml, 0.67 mmol) in toluene (2 ml) was added dropwise at 0 °C 1-methyl-2-pyrrolidone (0.08 ml, 0.75 mmol) and stirred for 30 min at this temperature. This solution was added at 0°C to a mixture of ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (cp. Example 23) (200 mg, 0.54 mmol) in toluene (2 ml) and the resulting mixture was stirred for 2 h at ambient temperature.It was concentrated in vacuo and stirred for 18 h in THF (5 ml). Further aluminate solution (to a mixture of sodiumdihydro-bis(2-methoxyethoxy)aluminate solution (3.5 M in toluene, 0.38 ml, 1.34 mmol) in THF (2 ml) was added dropwise at 0 °C 1-methyl-2-pyrrolidone (0.17 ml, 0.75 mmol) and stirred for 30 min at 0°C) was added and stirring was continued for 3 d at ambient temperature. The mixture was quenched with aqueous HCl (1 N, 10 ml) and stirred for 30 min at 65 °C. After cooling to 0 °C aqueous sodium carbonate (saturated, 10 ml) was added and it was extracted with ethyl acetate (20 ml). The organic layers were washed with brine, dried over sodium sulfate and were evaporated. Purification by chromatography (SiO_2, heptane:ethyl acetate:dichloromethane = 60:20:20 to 30:50:20) afforded the title compound (40 mg, 19%) as a white solid. MS: m/e = 404.3/406.2 $[M+H]^+$.

Example 26

1-[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-butan-1-one

To a solution of of 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol) in THF (10 ml) was added propylmagnesium bromide solution (2 M in THF, 0.30 mL, 0.60 mmol) at -78°C under an argon atmospher. After 5 min stirring at -78°C, the dry-ice-bath was removed and the reaction mixture was stirred for 4.5 h while allowing to warm to ambient temperature, followed by stirring for 23 h at 40 °C Further grignard-solution (1.60 mmol) was added and stirring continued for another 22 h at 60 °C. After cooling to 0 °C, aqueous HCl (1 M, 4.0 ml) was added and the mixture stirred for 1 h. Aqueous sodium carbonate (saturated, 8ml) was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine and werevaporated. Purification by chromatography (SiO_2, acetonitril:water:triethylamine = 9.5:90:0.5 to 94.5:5:0.5) afforded the title compound (28 mg, 38%) as an off-white solid. MS: m/e = 374.0 $[M+H]^+$.

Example 27

1-[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-pentan-1-one

As described for example 26, 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol), using butylmagnesium chloride solution (2 M in THF, 0.30 mL, 0.60 mmol) instead of propylmagnesium bromide solution, was converted to the title compound (22 mg, 28%) which was obtained as a white solid. MS: m/e = 388.0 $[M+H]^+$.

Example 28

1-[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-but-2(*E*)-en-1-one

As described for example 26, 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol), using 1-methyl-1-propenylmagnesium bromide solution (0.5 M in THF, 1.20 mL, 0.60 mmol) instead of propylmagnesium bromide solution, was converted to the title compound (23 mg, 30%) which was obtained as a light yellow solid. MS: m/e = 383.9 $[M+H]^+$.

Example 29

[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-o-tolyl-methanone

As described for example 26, 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol), using o-tolylmagnesium bromide solution (2 M in diethylether, 0.30 mL, 0.60 mmol) instead of propylmagnesium bromide solution, was converted to the title compound (24 mg, 29%) which was obtained as a light brown solid. MS: m/e = 421.9 $[M+H]^+$.

Example 30

1-[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-ethanone

As described for example 26, 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol), using methylmagnesium bromide solution (3 M in diethylether, 0.20 mL, 0.60 mmol) instead of propylmagnesium bromide solution, was converted to the title compound (10 mg, 15%) which was obtained as a light brown solid. MS: m/e = 346.0 $[M+H]^+$.

Example 31

1-[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-3-methyl-butan-1-one

As described for example 26, 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol), using iso-butylmagnesium chloride solution (2 M in diethylether, 0.30 mL, 0.60 mmol) instead of propylmagnesium bromide solution, was converted to the title compound (15 mg, 19%) which was obtained as a yellow oil. MS: m/e = 388.0 $[M+H]^+$.

Example 32

1-[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-2-phenyl-ethanone

As described for example 26, 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol), using benzylmagnesium chloride solution (1 M in diethylether, 0.60 mL, 0.60 mmol) instead of propylmagnesium bromide solution, was converted to the title compound (3 mg, 4%) which was obtained as a yellow oil. MS: m/e = 421.9 $[M+H]^+$.

Example 33

1-[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-3-phenyl-propan-1-one

As described for example 26, 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol), using phenethylmagnesium chloride solution (1 M in THF, 0.60 mL, 0.60 mmol) instead of propylmagnesium bromide solution, was converted to the title compound (4 mg, 5%) which was obtained as a light brown solid. MS: m/e = 436.0 $[M+H]^+$.

Example 34

[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-phenyl-methanone

As described for example 26, 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol), using phenylmagnesium bromide solution (1 M in THF, 0.60 mL, 0.60 mmol) instead of propylmagnesium bromide solution, was converted to the title compound (12 mg, 15%) which was obtained as a white solid. MS: m/e = 406.1 $[M+H]^+$.

Example 35

[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-thiophen-2-yl-methanone

As described for example 26, 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol), using thiophen-2-ylmagnesium bromide solution (2 M in THF, 0.30 mL, 0.60 mmol) instead of propylmagnesium bromide solution, was converted to the title compound (8 mg, 10%) which was obtained as a brown solid. MS: m/e = 411.9 $[M+H]^+$.

Example 36

1-[3-Bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-2-(3-chloro-phenyl)-ethanone

As described for example 26, 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid methoxy-methyl-amide (78 mg, 0.20 mmol), using 3-chlorobenzylmagnesium chloride solution (0.25 M in THF, 2.40 mL, 0.60 mmol) instead of propylmagnesium bromide solution, was converted to the title compound (4 mg, 5%) which was obtained as a light yellow solid. MS: m/e = 456.1 $[M+H]^+$.

Example 37

3-Fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid cyclopropyl-amide

As described for example 10, 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzo-diazepine-10-carboxylic acid (500 mg, 1.75 mmol), using cyclopropylamine instead of propargylamine, was converted to the title compound (329 mg, 58%) which was obtained as a white solid. MS: m/e = 325.3 $[M+H]^+$.

Example 38

Ethyl 3-(2,2,2-trifluoro-acetylamino)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

To a solution of ethyl 3-amino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (150 mg, 0.48 mmol) and N,N-diisopropyl ethyl amine (0.25 mL, 1.44 mmol) in dichloromethane (5 mL) was added dropwise at 15 °C trifluoroacetic anhydride (87 µL, 0.62 mmol). The reaction mixture was stirred for 30 min at ambient temperature before pouring onto aqueous sodium hydrogencarbonate (saturated) and extraction with dichloromethane, drying over sodium sulfate and concentration. Purification of the residue by chromatography (SiO_2,

dichloromethane:methanol = 40:1 to 15:1:) afforded the title compound (175 mg, 89%) as a yellow solid. MS: m/e = 407.1 $[M+H]^+$.

Example 39

Ethyl 3-isobutyrylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

To a solution of ethyl 3-amino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (150 mg, 0.48 mmol) and N,N-diisopropyl ethyl amine (0.25 mL, 1.44 mmol) in dichloromethane (5 mL) was added dropwise at 15 °C isobutyric acid chloride (65 µL, 0.62 mmol). The reaction mixture was stirred for 30 min at ambient temperature before pouring onto aqueous sodium carbonate (saturated) and extraction with dichloromethane, drying over sodium sulfate and concentration. Purification of the residue by chromatography (SiO_2, dichloromethane:methanol = 40:1 to 15:1:) afforded the title compound (178 mg, 97%) as an off-white solid. MS: m/e = 381.1 $[M+H]^+$.

Example 40

Ethyl 3-[(isoxazole-5-carbonyl)-amino]-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

As described for example 39, ethyl 3-amino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (150 mg, 0.48 mmol), using isoxazole-5-carbonyl chloride instead of isobutyric acid chloride, was converted to the title compound (105 mg, 54%) which was obtained as an off-white solid. MS: m/e = 406.2 $[M+H]^+$.

Example 41

Ethyl 3-(3-methoxy-propionylamino)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

As described for example 39, ethyl 3-amino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (150 mg, 0.48 mmol), using 3-methoxy-propionyl chloride instead of isobutyric acid chloride, was converted to the title compound (20 mg, 10%) which was obtained as an off-white solid. MS: m/e = 397.0 $[M+H]^+$.

Example 42

Ethyl 3-formylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

To formic acid (3.04 mL, 81 mmol) is added dropwise acetic anhydride (92 µL, 0.97 mmol) and the reaction mixture is stirred for 1 h at ambient temperature before adding

ethyl 3-amino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (100 mg, 0.32 mmol). After 2 h stiring at this temperature aqueous sodium hydrogencarbonate (half-saturated) was added and stirring was continued for 30 min. After extraction with dichloromethane/methanol (9:1), the combined organic layers were dried over sodium sulfate and concentrated. Crystallisation from methanol followed by recrystallisation from acetonitrile afforded the title compound (50 mg, 44%) which was obtained as a white solid. MS: m/e = 338.9 $[M+H]^+$.

Example 43

Ethyl 3-ethoxycarbonylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

As described for example 39, ethyl 3-amino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (110 mg, 0.35 mmol), using ethyl chloroformiate instead of isobutyric acid chloride, was converted to the title compound (90 mg, 66%) which was obtained as a white solid. MS: m/e = 382.2 $[M]^+$.

Example 44

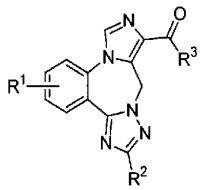
Ethyl 3-(3-ethyl-ureido)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate

A mixture of ethyl 3-amino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate (50 mg, 0.16 mmol), ethyl isocyanate (19 µL, 0.24 mmol) and triethylamine (17 µL, 0.16 mmol) in THF (4 mL) was heated to reflux for 4 h.The reaction mixture was poured onto water and was extracted with dichloromethane, dried over sodium sulfate and concentrated. Purification of the residue by chromatography (SiO_2, dichloromethane:methanol = 30:1 to 15:1:) afforded the title compound (18 mg, 29%) as a white solid. MS: m/e = 382.4 $[M+H]^+$.

2005293820 04 Sep 2009

The claims defining the invention are as follows:

1. The use of substituted imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine derivatives of the formula



I

R^1 is halogen, C_{1-7}-alkyl, C_{2-7}-alkynyl, cycloalkyl, C_{1-7}-alkoxy, OCF_3, -NHR, -NHC(O)R or $-NHSO_2R$;

R^2 is hydrogen, methyl or aryl, which is unsubstituted or substituted by one or two substituents, selected from the group consisting of halogen or C_{1-7}-alkoxy;

R^3 is hydrogen, C_{1-7}-alkyl, C_{2-7}-alkenyl, cycloalkyl, C_{1-7}-alkoxy, $-O(CH_2)_{n+1}-OC_{1-7}$alkyl, $-(CH_2)_n$-aryl, which is optionally substituted by C_{1-7}-alkyl or halogen, heteroaryl, -NHR, $-NR_2$, wherein R_2 may be the same or different, or is $-NHCH_2C{\equiv}CH$, or pyrrolidin-1-one;

R is hydrogen, C_{1-7}-alkyl, C_{1-7}-alkyl substituted by halogen, heteroaryl, $-(CH_2)_nO-C_{1-7}$-alkyl, $-NH-C_{1-7}$-alkyl, cycloalkyl or aryl,

n is 0, 1, 2 or 3;

and their pharmaceutically acceptable acid addition salts for the manufacture of medicaments for use as cognitive enhancers or for the treatment of cognitive disorders, anxiety, Alzheimer's disease or schizophrenia.

2. The use of compounds of formula I according to claim 1 for the manufacture of medicaments for the treatment of Alzheimer's disease.

3. The use of compounds of formula I according to claim 1, in which R^3 is C_{1-7}-alkyl.

4. The use of compounds of formula I according to claim 3, wherein the compounds are

1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-ethanone,

1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,

1-[3-Chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-butan-1-one or

1-[3-bromo-9H-imidazo[1 ,5-a][1 ,2,4]triazolo[1 ,5-d][1 ,4]benzodiazepin-10-yl]-3-methyl-butan-1-one.

5. The use of compounds of formula I according to claim 1, in which R^3 is cycloalkyl.

6. The use of compounds of formula I according to claim 5, wherein the compounds are

cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone,

cyclopropyl-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone or

cyclopropyl-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone.

7. The use of compounds of formula I according to claim 1, in which R^3 is $-(CH_2)_3$-phenyl.

8. The use of compounds of formula I according to claim 7, wherein the compound is

1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-4-phenyl-butan-1-one or

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-3-phenyl-propan-1-one.

9. The use of compounds of formula I according to claim 1, in which R^3 is ethoxy.

10. The use of compounds of formula I according to claim 9, wherein the compounds are

ethyl 3-cyclopropyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

ethyl 3-methoxy-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

ethyl 3-acetylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

ethyl 3-trifluoromethoxy-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

ethyl 3-ethynyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

ethyl 3-(2,2,2-trifluoro-acetylamino)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

ethyl 3-isobutyrylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

ethyl 3-(3-methoxy-propionylamino)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

ethyl 3-formylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

ethyl 3-ethoxycarbonylamino-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate or

ethyl 3-(3-ethyl-ureido)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate.

11. The use of compounds of formula I according to claim 1, in which R^3 is hydrogen.

12. The use of compounds of formula I according to claim 11, wherein the compound is

3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd or

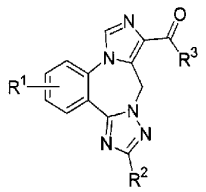
3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carbaldehyd.

13. The use of compounds of formula I according to claim 1, in which R^3 is $-NHCH_2C{\equiv}CH$.

14. The use of compounds of formula I according to claim 13, wherein the compound is

3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid prop-2-ynylamide.

15. Compounds of formula I-A, encompassed by compounds disclosed in formula I according to claim 1



I-A

wherein

wherein

R^1 is halogen, C_{1-7}-alkyl, C_{2-7}-alkynyl, cycloalkyl, C_{1-7}-alkoxy, OCF_3, -NHR, -NHC(O)R or $-NHSO_2R$;

R^2 is hydrogen, methyl or aryl, which is unsubstituted or substituted by one or two substituents, selected from the group consisting of halogen or C_{1-7}-alkoxy;

R^3 is C_{1-7}-alkyl, C_{2-7}-alkenyl, cycloalkyl, $-O(CH_2)_{n+1}-OC_{1-7}$alkyl, $-(CH_2)_n$-aryl, which is optionally substituted by C_{1-7}-alkyl or halogen, heteroaryl, -NHR, $-NR_2$, wherein R_2 may be the same or different, or is $-NHCH_2C{=}CH$, or pyrrolidin-1-one;

R is hydrogen, C_{1-7}-alkyl, C_{1-7}-alkyl substituted by halogen, heteroaryl, $-(CH_2)_nO-C_{1-7}$-alkyl, $-NH-C_{1-7}$-alkyl, cycloalkyl or aryl,

n is 0, 1, 2 or 3;

and their pharmaceutically acceptable acid addition salts.

16. Compounds of formula I-A according to claim 15, which compounds are

1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-ethanone,

1-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1 ,4]benzodiazepin-10-yl]-propan-1-one,

cyclopropyl-[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone,

1- [3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-4-phenyl-butan-1-one,

1- [3-chloro-9H-imidazo[1 ,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,

cyclopropyl-[3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-propan-1-one,

cyclopropyl-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-methanone,

1-[[3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]carbonyl]-2-pyrrolidinone,

3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid prop-2-ynylamide,

3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid benzylamide,

2-methoxy-ethyl 3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylate,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-butan-1-one,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-pentan-1-one,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-but-2(*E*)-en-1-one,

[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-o-tolyl-methanone,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-ethanone,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-3-methyl-butan-1-one,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-2-phenyl-ethanone,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-3-phenyl-propan-1-one,

[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-phenyl-methanone,

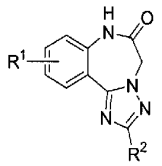
[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepin-10-yl]-thiophen-2-yl-methanone,

1-[3-bromo-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1 ,4]benzodiazepin-10-yl]-2-(3-chloro-phenyl)-ethanone or

3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine-10-carboxylic acid cyclopropyl-amide.

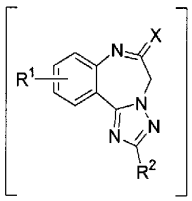
17. A process for preparation of compounds of formula I-A as defined in claim 15, which process comprises

a) reacting a compound of formula



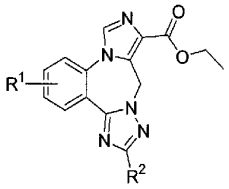
II

with an activating agent, such as phosphorous oxide chloride (for X = Cl) or with diphenylphosphorylchloride (for X = -OP(O)(OPh)$_2$) to a compound of formula



III

which may be isolated or may be directly reacted with a mixture of lithium diisopropylamide or lithium hexamethyldisilazide and (E)-(dimethylamino-methylamino)-acetic acid ethyl ester or ethylisocyanoacetate to a compound of formula

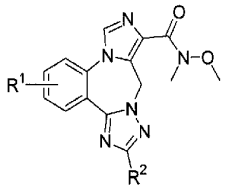


I-1

wherein R^1 and R^2 have the meaning as described in claim 1, or

b) reacting a compound of formula

2005293820 04 Sep 2009

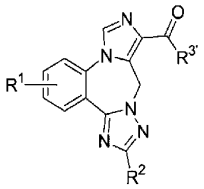


IV

with a compound of formula

$R^{3'}MgX$

to a compound of formula

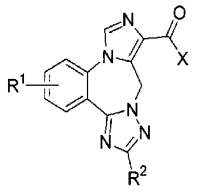


I-2

wherein $R^{3'}$ is C_{1-7}-alkyl, C_{2-7}-alkenyl, cycloalkyl, $-(CH_2)_n$-aryl, optionally substituted by C_{1-7}-alkyl or halogen, heteroaryl, and R^1 and R^2 are as described in claim 1,

or

c) reacting a compound of formula



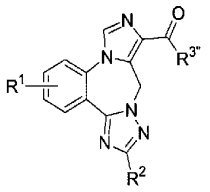
V

with a compound of formula

NH_2R, NHR_2, wherein R_2 may be the same or different, $NH_2CH_2C{\equiv}CH$, pyrrolidin-1-one or $HO(CH_2)_{n+1}$-O-C_{1-7}-alkyl,

to a compound of formula

2005293820 04 Sep 2009

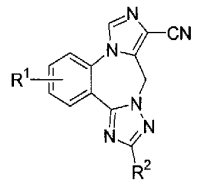


I-3

wherein $R^{3"}$ is -NHR, $-NR_2$, wherein R_2 may be the same or different, or is -$NHCH_2C{\equiv}CH$, pyrrolidin-1-one or $O(CH_2)_{n+1}$-O-C_{1-7}-alkyl, and R^1 and R^2 are as described in claim 1,

or

d) reacting a compound of formula

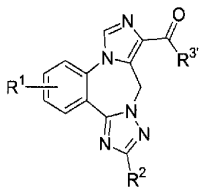


VI

with a compound of formula

$$R^{3'}MgX$$

to a compound of formula



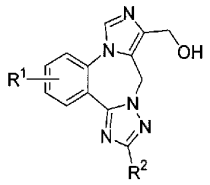
I-2

wherein $R^{3'}$ is C_{1-7}-alkyl, C_{2-7}-alkenyl, cycloalkyl, $-(CH_2)_n$-aryl, optionally substituted by C_{1-7}-alkyl or halogen, heteroaryl, and R^1 and R^2 are as described in claim 1,

or

e) reacting a compound of formula

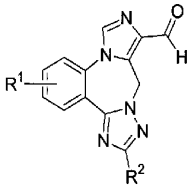
2005293820 04 Sep 2009



VII

with manganese (IV) oxide

to an aldehyde of formula



I-4

wherein R^1 and R^2 are as described above,

and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

18. A compound of formula I-A according to claim 15, whenever prepared by a process as claimed in claim 17.

19. A medicament containing one or more compounds of formula I-A according to claim 15 and pharmaceutically acceptable excipients.

20. A medicament according to claim 19 for use as a cognitive enhancer or for the treatment of cognitive disorders, Alzheimer's disease, anxiety or schizophrenia.

21. A medicament according to claim 20 for the treatment of Alzheimer's disease.

Dated 3 September, 2009

F. Hoffmann-La Roche AG

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON