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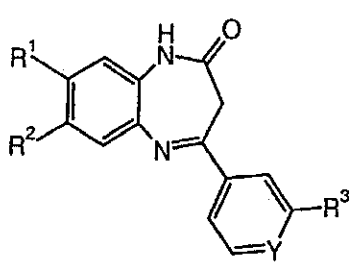
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(54) Title: DIHYDRO-BENZO[b][1,4]DIAZEPIN-2-ONE DERIVATIVES AS MGLUR2 ANTAGONISTS I

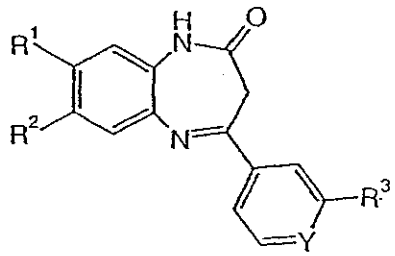


(I)

(57) Abstract: This invention is concerned with dihydro-benzo[b][1,4]diazepin-2-one derivatives of general formula (I) wherein R^1, R^2, R^3 and Y are as defined in the specification. The invention further relates to medicaments containing these compounds, a process for their preparation as well as their use for preparation of medicaments for the treatment or prevention of acute and/or chronic neurological disorders.

Dihydro-benzo[b][1,4]diazepin-2-one derivatives as mGluR2 antagonists I

A first aspect of the present invention provides compounds of general formula I



I

wherein

R^1 is cyano,
fluoro-lower alkyl,
lower alkoxy,
fluoro-lower alkoxy,
or is pyrrol-1-yl, which is unsubstituted or substitued by one to three substituents
selected from the group consisting of
fluoro, chloro, cyano, phenyl, optionally substituted by halogen,
$-(CH_2)_{1-4}$-hydroxy, fluoro-lower alkyl, lower alkyl, $-(CH_2)_n$-lower alkoxy,
$-(CH_2)_n$-C(O)O-R", $-(CH_2)_{1-4}$-NR'R", hydroxy-lower alkoxy and
$-(CH_2)_n$-CONR'R";

R^2 is hydrogen, if R^1 is optionally substituted pyrrol-1-yl as defined above, or is
halogen,
hydroxy,
lower alkyl,
fluoro-lower alkyl,
lower alkoxy,
hydroxymethyl,
hydroxyethoxy,
lower alkoxy-$(ethoxy)_n$ (n = 1 to 4),
lower alkoxymethyl,
cyanomethoxy,

morpholine-4-yl,
thiomorpholine-4-yl,
1-oxothiomorpholine-4-yl,
1,1-dioxothiomorpholine-4-yl,
4-oxo-piperidine-1-yl
4-alkoxy-piperidine-1-yl,
4-hydroxy-piperidine-1-yl,
4-hydroxyethoxy-piperidine-1-yl,
4-lower alkyl-piperazine-1-yl,
alkoxycarbonyl,
2-dialkylamino-ethylsulfanyl,
N,N-bis lower alkylamino lower alkyl,
carbamoylmethyl,
alkylsulfonyl
lower alkoxycarbonyl-lower alkyl,
alkylcarboxy-lower alkyl,
carboxy-lower alkyl,
alkoxycarbonylmethylsulfanyl,
carboxymethylsulfanyl,
1,4-dioxa-8-aza-spiro[4.5]dec-8-yl,
carboxy-lower alkoxy,
cyano-lower alkyl,
2,3-dihydroxy-lower alkoxy,
carbamoylmethoxy,
2-oxo-[1,3]-dioxolan-4-yl-lower alkoxy,
N-(2-hydroxy-lower alkyl)-N-lower alkyl amino,
hydroxycarbamoyl-lower alkoxy,
2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5c]-pyrrol-5-yl,
lower alkoxy-carbamoyl-lower alkoxy,
3R-hydroxy-pyrrolidin-1-yl,
3,4-dihydroxy-pyrrolidin-1-yl,
2-oxo-oxazolidin-3-yl,
lower alkyl-carbamoylmethoxy or
aminocarbamoyl-lower alkoxy;

Y is –CH= or =N-;

R^3 is halogen,
lower alkyl,
fluoro-lower alkyl,
lower alkoxy,
cyano,
$-(CH_2)_n-C(O)-OR''$,
$-(CH_2)_n-C(O)-NR'R''$,
or is an optionally substituted five-membered aromatic heterocycle, which may be substituted by halogen, fluoro-lower alkyl, fluoro-lower alkoxy, cyano, $-(CH_2)_n-NR'R''$, $-(CH_2)_n-C(O)-OR''$, $-(CH_2)_n-C(O)-NR'R''$, $-(CH_2)_n-SO_2-NR'R''$, $-(CH_2)_n-C(NH_2)=NR''$, hydroxy, lower alkoxy, lower alkylthio, or by lower alkyl, which is optionally substituted by fluoro, hydroxy, lower alkoxy, cyano or carbamoyloxy;

R' is hydrogen,
lower alkyl,
C_3-C_6-cycloalkyl,
fluoro-lower alkyl or
2-lower alkoxy lower alkyl;

R'' is hydrogen,
lower alkyl,
C_3-C_6-cycloalkyl,
fluoro-lower alkyl,
2-lower alkoxy lower alkyl,
$-(CH_2)_{2-4}$-di-lower alkylamino,
$-(CH_2)_{2-4}$-morpholinyl,
$-(CH_2)_{2-4}$-pyrrolidinyl,
$-(CH_2)_{2-4}$-piperidinyl or
3-hydroxy-lower alkyl;

n is 0, 1, 2, 3 or 4;

and to their pharmaceutically acceptable addition salts.

It has surprisingly been found that the compounds of general formula I are metabotropic glutamate receptor antagonists. Compounds of formula I are distinguished by valuable therapeutic properties.

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

L-glutamic acid, the most commonly occurring neurotransmitter in the CNS, plays a critical role in a large number of physiological processes. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) form the second main group and, furthermore, belong to the family of G-protein-coupled receptors.

At present, eight different members of these mGluR are known and of these some even have sub-types. On the basis of structural parameters, the different influences on the synthesis of secondary metabolites and the different affinity to low-molecular weight chemical compounds, these eight receptors can be sub-divided into three sub-groups: mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the group II can be used for the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are chronic and acute pain, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depressions.

Objects of the present invention are compounds of formula I and their pharmaceutically acceptable salts per se and as pharmaceutically active substances, their manufacture, medicaments based on a compound in accordance with the invention and their production, as well as the use of the compounds in accordance with the invention in the control or prevention of illnesses of the aforementioned kind, and, respectively, for the production of corresponding medicaments.

The compounds of formula I can also be used in form of their prodrugs. Examples are esters, N-oxides, phosphate esters, glycoamide esters, glyceride conjugates and the like. The prodrugs may add to the value of the present compounds advantages in absorption, pharmacokinetics in distribution and transport to the brain.

All tautomeric forms of the compounds of the invention are also embraced herewith.

Preferred compounds of formula I in the scope of the present invention are those, wherein R^1 is trifluoromethyl. Exemplary preferred are compounds, wherein R^2 is morpholine, for example the following compounds:

4-(8-morpholin-4-yl-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile,

4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-[3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-[3-(3-hydroxymethyl-isoxazol-5-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one, and

4-[3-(5-hydroxymethyl-isoxazol-3-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

Also preferred are compounds of formula I, wherein R^1 is trifluoromethyl and R^2 is thiomorpholine. The following are examples of such compounds:

4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-7-thiomorpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one, and

4-(4-oxo-8-thiomorpholin-4-yl-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile.

Further preferred are compounds of formula I wherein R^1 is trifluoromethyl and R^2 is lower alkoxy. Examples of such compounds are the following:

7-methoxy-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-methoxy-4-[3-(5-pyrrolidin-1-ylmethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-(8-ethoxy-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile,

4-[3-(5-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-7-ethoxy-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-ethoxy-4-(3-{5-[(2,2,2-trifluoro-ethylamino)-methyl]-[1,2,3]triazol-1-yl}-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-ethoxy-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one, and

7-methoxy-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

Also preferred are compounds of formula I, wherein R^1 is trifluoromethyl and R^2 is lower alkyl or halogen. The following are examples of such compounds:

4-(8-methyl-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile,

7-chloro-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-chloro-4-[3-(5-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-[3-(5-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-methyl-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-chloro-4-(3-[1,2,4]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-chloro-4-(3-imidazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-chloro-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-methyl-4-(3-[1,2,4]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-(3-imidazol-1-yl-phenyl)-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-methyl-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-[3-(2-hydroxymethyl-5-methyl-thiazol-4-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one, and

4-[3-(4-hydroxymethyl-thiazol-2-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

Further preferred are compounds of formula I, wherein R^1 is unsubstituted pyrrol-1-yl. Exemplary preferred are compounds, wherein R^2 is hydrogen, halogen, lower alkoxy-ethoxy or lower alkoxy, for example the following compounds:

4-(3-iodo-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-(3-imidazol-1-yl-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-[3-(4-hydroxymethyl-thiazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

8-pyrrol-1-yl-4-(3-[1,2,3]triazol-1-yl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-(3-oxazol-2-yl-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

5-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid ethyl ester,

4-[3-(4-hydroxymethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one, and

4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

Further preferred are compounds of formula I, wherein R^1 is substituted pyrrol-1-yl. Exemplary preferred are compounds, wherein R^2 is hydrogen or lower alkoxy, for example the following compounds:

4-(2-chloro-phenyl)-1-[2-(3-cyano-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-7-yl]-1H-pyrrole-3-carbonitrile,

3-[4-oxo-7-(3-phenyl-pyrrol-1-yl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile, and

3-[7-(2-tert.-butyl-pyrrol-1-yl)-8-methoxy-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile.

Further preferred are compounds, wherein R^1 is cyano.

Preferred are further compounds, wherein R^2 is morpholine or thiomorpholine. Preferred compounds of formula I in the scope of the present invention are further those, wherein R^3 is cyano or an optionally substituted five-membered aromatic heterocycle, which may be substituted by $-CH_2OH$.

The term "lower alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1-7 carbon atoms, preferably with 1-4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and the like.

The term "lower alkoxy" denotes a lower alkyl residue in the sense of the foregoing definition bound via an oxygen atom. Examples of "lower alkoxy" residues include methoxy, ethoxy, isopropoxy and the like.

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

The term "fluoro-lower alkyl" means a lower alkyl residue, wherein one or more hydrogen-atoms may be replaced by fluoro.

The term "fluoro-lower alkoxy" denotes a lower alkoxy residue in the sense of the definition herein before, wherein one or more hydrogen-atoms may be replaced by fluoro.

"Lower alkoxy-$(ethoxy)_m$" (m is 1, 2, 3 or 4) denotes a lower alkoxy residue in the sense of the foregoing definition bound via 1 to 4 $-CH_2-CH_2-O-$ groups, for example 2-methoxy-ethoxy.

The term "C_3-C_6-cycloalkyl" means a cycloalkyl group containing 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "alkylthio" denotes a lower alkyl residue in the sense of the foregoing definition bound via an sulfur atom, for example methylsulfanyl.

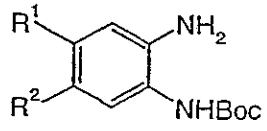
The expression "five-membered aromatic heterocycle" embraces furane, thiophene, thiazole, pyrrole, imidazole, pyrazole, oxazole, isoxazole, triazole, oxadiazole, thiadiazole and tetrazole. Preferred heterocycles are 1,2,3-triazole, isoxazole, 1,3-oxazole, 1,3-thiazole, 1,3,4-oxadiazole or imidazole.

"Optionally substituted" means that a group may or may not be substituted with one or more, preferably one or two substituents independently selected from the specified group.

The term "pharmaceutically acceptable addition salt" refers to any salt derived from an inorganic or organic acid or base.

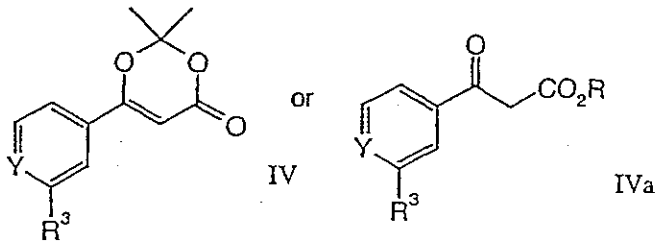
A second aspect of the present invention provides a process for preparing compounds of formula I as defined in the first aspect, which process comprises

a) reacting a compound of formula II



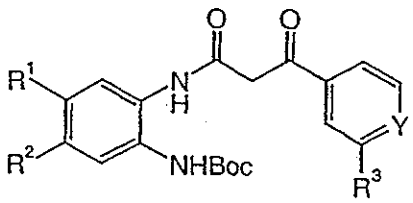
II

with a compound of formula IV or IVa



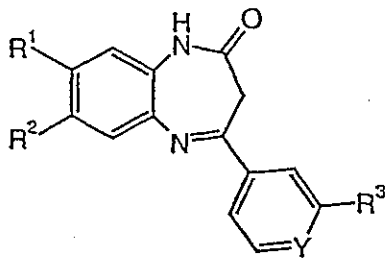
IV or IVa

wherein R is lower alkyl, prefereably ethyl or tert.-butyl, to a compound of formula III



III

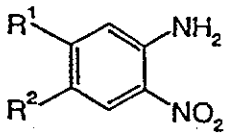
which subsequently undergoes deprotection of the amino group and cyclization, to obtain a compound of formula I



I

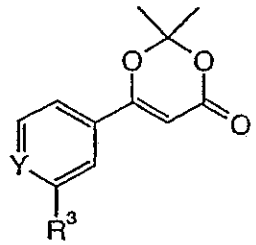
wherein R^1, R^2, R^3 and Y are as described above, or

b) reacting a compound of formula VI



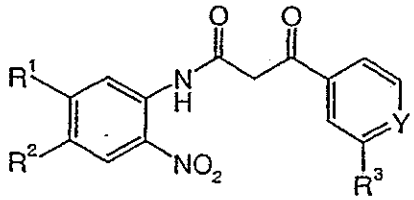
VI

with a compound of formula IV



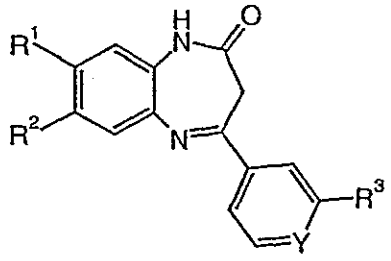
IV

to a compound of formula V



V

which subsequently undergoes reduction of the nitro group and cyclization, to obtain a compound of formula I



I

wherein R^1, R^2, R^3 and Y are as described above and, if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

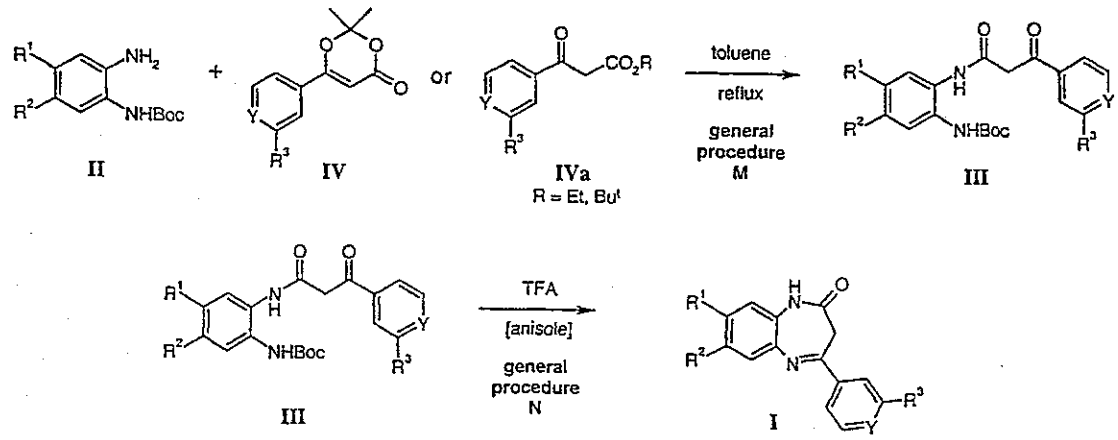
A third aspect of the present invention provides a medicament containing one or more compounds of the first aspect and pharmaceutically acceptable excipients.

A fourth aspect of the present invention provides a compound according to the first aspect, whenever prepared by a process of the second aspect or by an equivalent method.

A fifth aspect of the present invention provides a compound of the first aspect for the treatment or prevention of diseases.

A sixth aspect of the present invention provides the use of one or more compounds of the first aspect and/or one or more of their pharmaceutically acceptable acid addition salts for the manufacture of medicaments for the treatment or prevention of accute and/or chronic neurological disorders including psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits.

Scheme A



According to scheme A, compounds of general formula I, in which Y, R^1, R^2 and R^3 are as described above, can be prepared from compounds of general formula II via an acylation-deprotection-cyclization sequence:

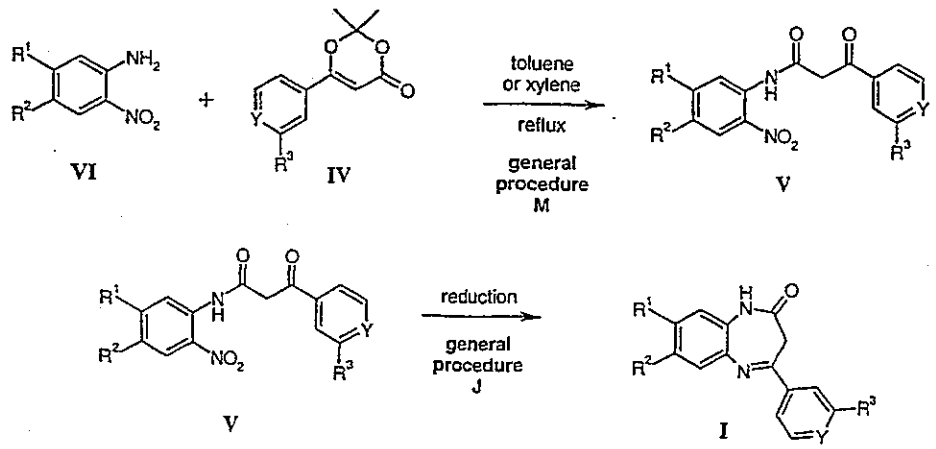
For example reacting compounds of general formula II with a dioxinone IV, in which Y and R^3 are as described above, in an inert solvent such as toluene or xylene at elevated temperatures, preferably between 80 °C and 160 °C gives rise to compounds of general formula III.

Alternatively, compounds of general formula III can also be prepared by for example reaction of a compound of general formula II with a β-ketoester (general formula IVa), in which Y and R^3 are as described above using the same conditions as described for the reaction with the dioxinones.

Afterwards, cleaving the BOC protecting group in compounds of general formula III and concomitant cyclization of the deprotected compound yields the desired compounds of general formula I. Any other suitable amino protecting group, such as e.g. Fmoc or benzyloxycarbonyl (Z), can be alternatively used instead of the BOC group.

The deprotection-cyclization step can be carried out by treating the compounds of general formula III with for example a Bronsted acid such as trifluoroacetic acid (TFA) in an inert solvent such as dichloromethane (DCM). The reaction is preferably carried out at temperatures between 0 °C and 50 °C. It may be advantageous to use also anisole or 1,3-dimethoxybenzene as a carbocation scavenger in the reaction mixture.

Scheme B

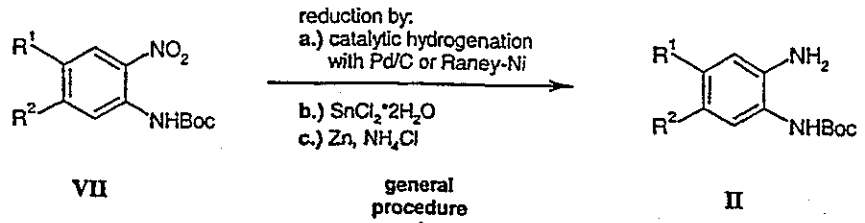


VI IV V V I

In addition, compounds of general formula I, in which Y, R^1, R^2 and R^3 are as described above, can be prepared according to scheme B, by for example reducing the nitro group in compounds of general formula V to the amino group and subsequent heating of the reaction mixture to achieve the cyclization. The reduction can for example be carried out using hydrogen gas in presence of a suitable catalyst like for example Raney-Nickel. Other possible reduction methods are using tin(II)chloride ($SnCl_2 \cdot 2H_2O$) in ethanol at temperatures between 70 °C and 80 °C, iron-powder and acetic acid in mixtures of THF, water and ethanol at temperatures between 50 °C and 80 °C, and also zinc-powder in the presence of ammonium chloride at temperatures between 20 °C and 80 °C. The exact conditions for the respective compounds of general formula I can be found in the experimental part.

Compounds of general formula V, in which Y, R^1, R^2 and R^3 are as described above, can be prepared according to scheme B by for example reacting a compound of general formula VI, with a dioxinone (general formula IV) in an inert solvent like for example toluene or xylene at elevated temperatures, preferably between 80 °C and 160 °C.

Scheme C

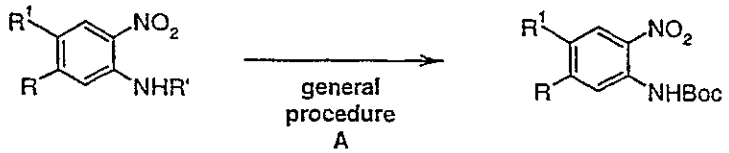


VII II

Compounds of general formula II, in which R^1 and R^2 are as described above, can be prepared according to scheme C by reducing the nitro group in compounds of general formula VII, in which R^1 and R^2 are as described above, to the amino group. The reduction can for example be carried out using hydrogen gas in presence of a suitable catalyst like for example Raney-Nickel or Palladium on carbon. Another possible reduction method is using tin(II)chloride ($SnCl_2 \cdot 2H_2O$) in ethanol at temperatures between 70 °C and 80 °C (as described in *Tetrahedron Lett.* 1984, *25*, 839), or alternatively in polar aprotic solvents, like DMF, DMA or NMP and the like, optionally in the presence of bases, like for example pyridine or triethylamine and the like, at temperatures between 0 °C and 80 °C. Another suitable method is using zinc-powder in the presence of ammonium chloride in protic solvents like for example water or ethanol at temperatures between 20 °C and 80 °C. The exact conditions for the respective compounds of general formula II can be found in the experimental part.

Compounds of general formula VII, in which R^1 and R^2 are as described above, can be prepared by different routes depending on the individual residues R^1 and R^2.

Scheme D



VIa R = Cl, F; R' = H
IXa R = Cl, F; R' = Ac

VIIa
R = Cl, F

R' = H: GP A, method a: diphosgene, EtOAc, 77 °C; then t-BuOH
R' = H: GP A, method b: Boc_2O, Cs_2CO_3, 2-butanone, 52 °C
R' = H: GP A, method c: i) Boc_2O, DMAP, THF; ii) TFA, DCM, 0 °C
R' = Ac: GP A, method d: i) Boc_2O, DMAP, THF; ii) NH_4OH, THF

As described in scheme D, compounds of the general formula VIIa, in which R^1 is as described above, R is chloro or fluoro and R' is hydrogen, can be prepared by protection of the amino group of compounds of the general formula VIa, in which R^1 is as described above, R is chloro or fluoro and R' is hydrogen, with a tert.-butoxycarbonyl-group (BOC). One possibility for the protection of the amino function is for example reacting compounds of general formula VIa with di-tert.-butyl-carbonate in the presence of a base such as cesium carbonate. The reaction can be carried out in polar solvents such as acetone or butanone and the like at temperatures between 20 °C and 80 °C.

Alternatively, the protection of the amino group can be achieved by preparing the intermediate isocyanate by treatment of compounds of the general formula VIa, , in which R^1 is as described above, R is chloro or fluoro and R' is hydrogen, with diphosgene, preferably in aprotic solvents such as EtOAc or 1,4-dioxane at temperatures from 0 °C to 100 °C, and subsequent treatment of the isocyanate with tert.-butanol in solvents such as dichloromethane or 1,2-dichloroethane and the like at temperatures between 20 °C and 85 °C to give the desired compounds of general formula Va.

Another suitable method to achieve this protection step is the intermediate formation of a di-BOC compound by treatment of compounds of the general formula VIa, , in which R^1 is as described above, R is chloro or fluoro and R' is hydrogen, with di-tert.-butyl-carbonate in the presence of DMAP in an aprotic solvent such as tetrahydrofuran and the like, followed by selective removal of a single BOC-group by treatment with a Bronsted-acid, like e.g. TFA, in aprotic solvents such as dichloromethane, chloroform or 1,2-dichloroethane at temperatures between 0 °C and 20 °C to give the desired compounds of general formula Va.

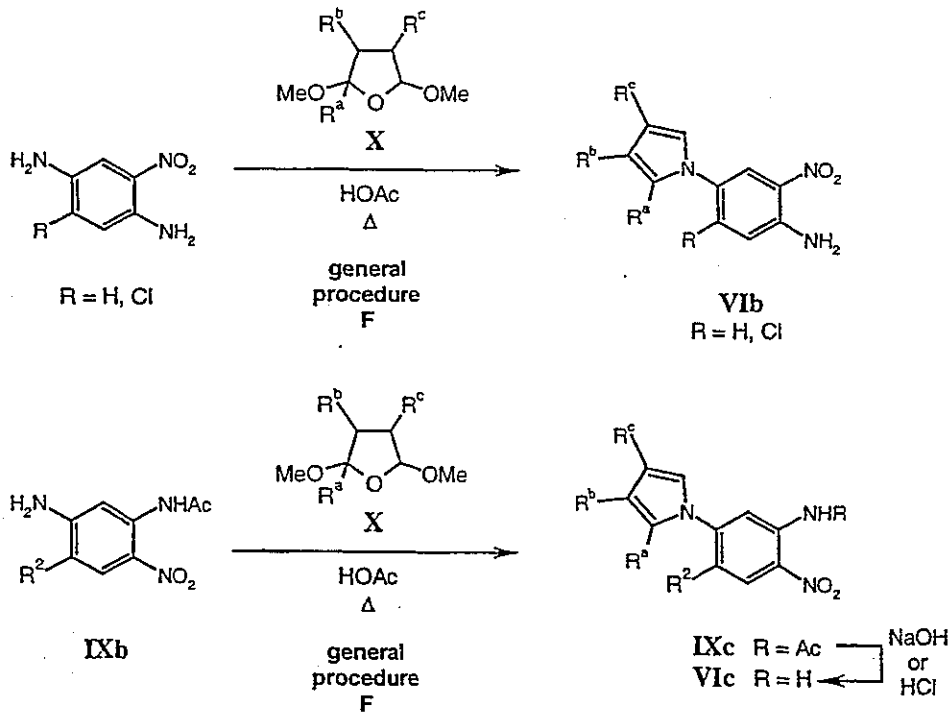
Yet another suitable method to produce compounds of general formula IXa is the intermediate formation of a N-Ac-BOC compound by treatment of compounds of the general formula VIa, in which R^1 is as described above, R is chloro or fluoro and R' is acetyl, with di-tert.-butyl-carbonate in the presence of DMAP in an aprotic solvent such as tetrahydrofuran and the like, followed by selective removal of a single BOC-group by treatment with a Bronsted-base, like e.g. aqueous ammonia (NH_4OH), in aprotic solvents such as tetrahydrofuran, diethylether or 1,4-dioxane and the like, at temperatures between 0 °C and 20 °C to give the desired compounds of general formula Va.

Apparently, the protection of the amino function as shown in scheme D can be applied to a number of commercially available starting materials or compounds synthesized by standard transformations [e.g. nitration followed by selective ammonolysis of the halide in ortho-position to the newly introduced nitro-group as described in *J. Med. Chem.* 1994, *37*, 467; or ortho-nitration of acetanilide-compounds followed by deacetylation with for example aqueous potassium hydroxide solution or aqueous hydrochloric acid as described in *Org. Synth.* 1945, *25*, 78 or in *J. Med. Chem.* 1985, *28*, 1387] known to anyone skilled in the art to produce the corresponding 2-nitroanilines with the general formula VIa, in which R^1 is as described above, R is chloro or fluoro and R' is hydrogen, or 2-nitroacetanilides with the general formula IXa, in which R^1 is as described above, R is chloro or fluoro and R' is acetyl. The exact

conditions for the respective compounds used in this invention can be found in the experimental part.

According to scheme E, compounds of general formula VIb, in which R^1 is pyrrol-1-yl optionally substituted as described above, and R is hydrogen or chloro, can be prepared from commercially available 2-nitro-1,4-phenylenediamine [CAS-No. 5307-14-2] [for R = H] or known 5-chloro-2-nitro-1,4-phenylenediamine [CAS-No. 26196-45-2] [for R = Cl] by selective condensation of the 4-amino-group with a suitable substituted 2,5-dimethoxytetrahydrofuran with the general formula X, as described in *J. Heterocycl. Chem.* 1988, *25*, 1003.

Scheme E



The reaction is preferably carried out in acidic media, like for example acetic acid or propionic acid and the like, at temperatures between 40 °C to 120 °C. The exact conditions for the respective compounds can be found in the experimental part.

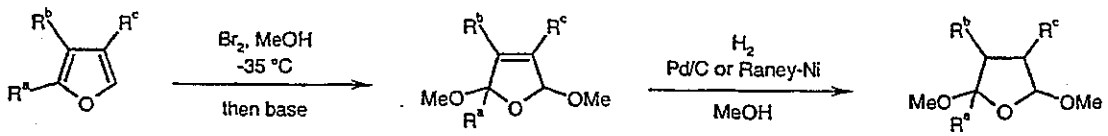
Also according to scheme E, compounds of the general formula VIc, in which R^1 is pyrrol-1-yl and optionally substituted as described above and R^2 is also as described above, can be prepared from N-(5-amino-2-nitro-phenyl)-acetamide-compounds of the general formula IXb, in which R^2 is as described above, by performing the same condensation reaction of the 5-amino-group with a suitable substituted 2,5-dimethoxytetrahydrofuran with the general formula X as described for the reaction with the 2-nitro-1,4-phenylenediamine. The deacetylation of the compounds of

general formula IXc, in which R^1 is pyrrol-1-yl and optionally substituted as described above and R^2 is also as described above, to produce compounds of the general formula VIc, in which R^1 is pyrrol-1-yl and optionally substituted as described above and R^2 is also as described above, can be done by standard acidic or basic hydrolysis reaction known to someone skilled in the art and the exact conditions for the respective compounds used in this invention can be found in the experimental part.

The synthesis of the corresponding N-(5-amino-2-nitro-phenyl)-acetamides with the general formula IXb, in which R^2 is as described above, follows standard procedures known to someone skilled in the art and the exact conditions for the respective compounds used in this invention can be found in the experimental part.

The corresponding substituted 2,5-dimethoxytetrahydrofurans with the general formula X, in which R^a, R^b and R^c are as described above in the general claim for the pyrrol-1-yl compounds, are either commercially available, or synthesized from the suitable substituted furan, as shown in scheme F. The corresponding substituents can optionally be protected with suitable protecting groups, known to someone skilled in the art, or alternatively can be introduced after the pyrrol ring synthesis. The two-step sequence consists of reacting the furan with bromine in MeOH at low temperature, like for example –35 °C, followed by treatment with base, like for example triethyl-amine and the like or potassium carbonate or sodium hydrogen carbonate and the like. The resulting 2,5-dimethoxydihydrofuran with the general formula VIII, in which R^a, R^b and R^c are as described above, can be reduced by catalytic hydrogenation, preferably in MeOH with catalysts like for example Palladium on carbon or Raney-Nickel and the like, to produce the desired 2,5-dimethoxytetrahydrofurans with the general formula X. An example for this sequence can be found in *Tetrahedron* 1971, *27*, 1973-1996.

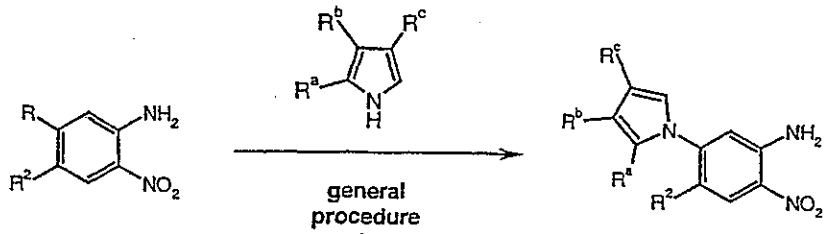
Scheme F



VIII X

The exact conditions for the individual compounds to be synthesized can be found in the experimental part.

Scheme G



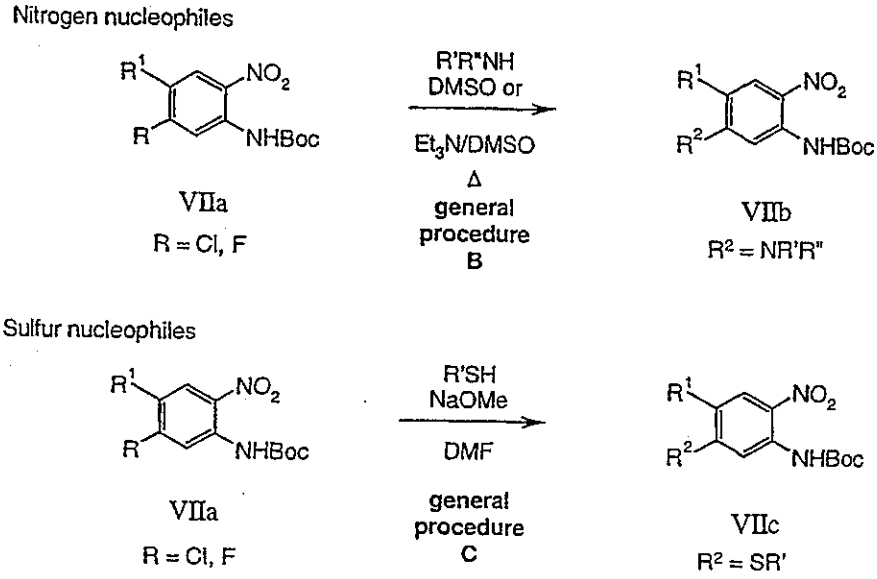
VId
R = Cl, F

VIc

Another method of preparing compounds with the general formula VIc, in which R^1 is pyrrol-1-yl, optionally substituted as described above, is by nucleophilic substitution reaction of compounds of the general formula VId, in which R is chloro or fluoro and R^2 is as described above, with the corresponding pyrrol as shown in scheme F. The reaction is preferably carried out in a polar, aprotic solvent such as dimethyl formamide, N-methyl–pyrrolidone or dimethyl sulfoxide and the like. The base can be selected from the sterically hindered amines such as triethylamine or Hünig's base, alkoxides such as sodium methoxide and tert.-butoxide, or hydrides such as sodium hydride. The reaction can be performed at temperatures between 20 °C and 110 °C, depending on the individual compounds to be synthesized. The exact conditions for the respective compounds used in this invention can be found in the experimental part.

As shown in scheme H, compounds of general formula VIIb and VIIc, in which R^2 is attached via a sulfur- or nitrogen-atom, respectively, and substituted with R' and R" as described above, can be prepared from compounds with the general formula VIIa, in which R^1 is as described as above and R is chloro or fluoro, by a nucleophilic substitution reaction with the respective amines or mercaptanes in the presence of a suitable base.

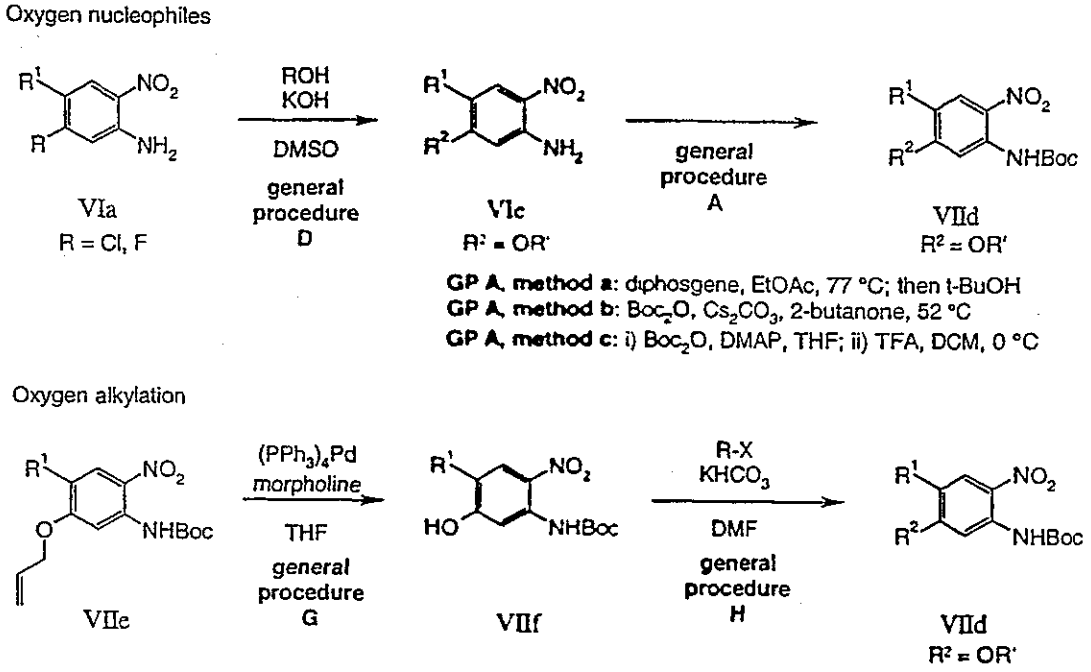
Scheme H



The reaction is preferably carried out in a polar, aprotic solvent such as dimethyl formamide, N-methyl–pyrrolidone or dimethyl sulfoxide and the like. The base can be selected from the sterically hindered amines such as triethylamine or Hünig's base, alkoxides such as sodium methoxide and tert.-butoxide, or hydrides such as sodium hydride. The reaction can be performed at temperatures between 20 °C and 110 °C, depending on the individual compounds to be synthesized.

As shown in scheme I, compounds of general formula VIId, in which R^2 is attached via an oxygen atom and R' is as described as above, can be prepared from compounds of the general formula VIa, in which R^1 is as described above and R is chloro or fluoro, by a nucleophilic aromatic substitution reaction with the respective alcohol (R'OH) in the presence of a suitable base to produce compounds of the general formula VIe, where the protection of the amino function can be performed as described earlier. The base can be selected from the class of Bronsted bases such as potassium hydroxide and the like. The reaction is preferably carried out in a polar, aprotic solvent such as dimethyl formamide, N-methyl–pyrrolidone or dimethyl sulfoxide and the like at temperatures between 20 °C and 100 °C.

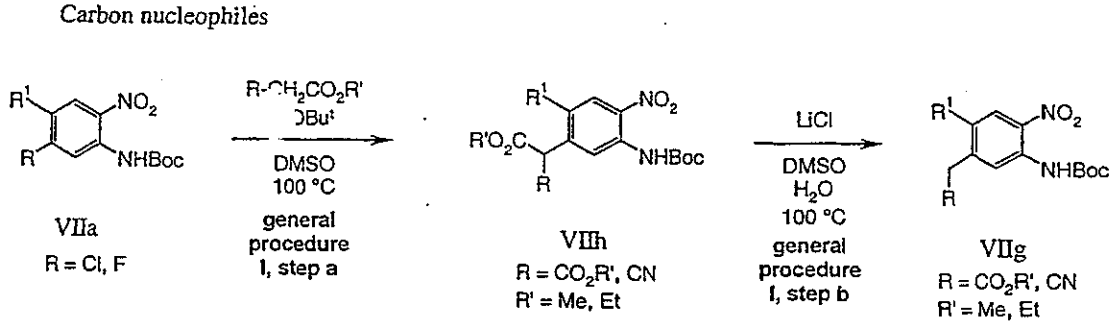
Scheme I



Yet another method of preparing compounds of the general formula VIId is using O-allyl compounds with the general formula VIIe, in which R^1 is as described above, and perfoming a deallylation-alkylation sequence as outlined in scheme I. The deallylation is preferably carried out by transition-metal catalyzed isomerisation, e.g. in the presence of Rhodium(I)-salts like for example Wilkinson's catalyst $[(PPh_3)_3RhCl]$ or Palladium(II)-salts such as $[(PPh_3)_2PdCl_2]$, followed by aqueous acid hydrolysis of the resulting vinyl ether. An example for this procedure can be found in *J. Org. Chem.* 1973, 38, 3224. Another method for the deallylation is the reaction with Palladium(0)-complexes such as $[(PPh_3)_4Pd]$ in the presence of excess of a secondary amine, as for example morpholine, as described for example in *Synthesis* 1996, 755. The alkylation of the resulting phenols with the general formula VIIf, in which R^1 is as described above, to the desired compounds of the general formula VIId can be carried out with electrophilic reagents of the general formula R-X, in which R has the meaning of lower alkyl, lower alkenyl, alkyl acetate or benzyl and X represents a leaving group, for example iodide, bromide, methanesulfonate or tolylsulfonate, in a suitable solvent in the presence of a base. The reaction is preferably carried out in polar, aprotic solvents, for example chlorinated solvents such as dichloromethane, chloroform or dichloroethane, or amides, for example dimethylformamide, dimethylacetamide and N-methyl-pyrrolidone, or sulfoxides, for example dimethyl sulfoxide. The base can be selected from the sterically hindered amines such as Hünig's base, alkoxides such as sodium methoxide and tert.-butoxide, hydrides such as sodium hydride, hydroxides

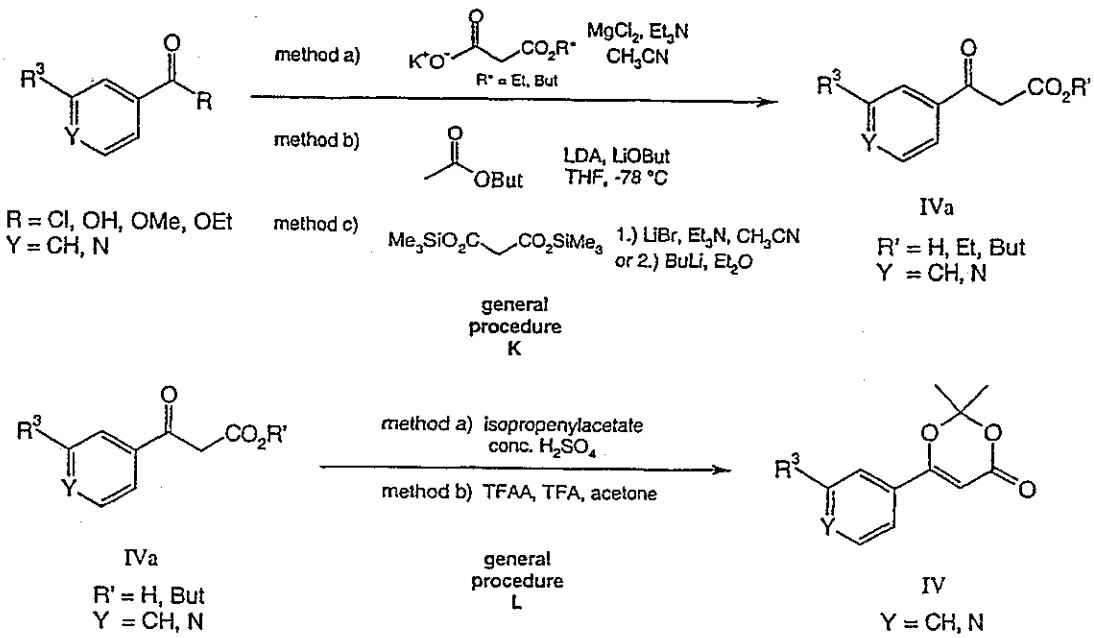
such as potassium hydroxide, carbonates such as potassium carbonate or hydrogen carbonates such as potassium hydrogen carbonate. The reaction can be performed at temperatures between -20 °C and 80 °C, depending on the individual compounds to be synthesized. For the synthesis of the O-tert.-butyl compounds with the general formula VIId, in which R^1 is as described above and R^2 is tert.-butoxy, the phenols with the general formula VIIf can be treated with DMF-di-tert.-butylacetal in toluene or benzene at 80 °C as described in *Synthesis* 1983, 135.

Scheme J



According to synthetic scheme J, compounds of general formula VIIg, in which R^2 is attached via a carbon atom and is as described above, can be prepared from compounds with the general formula VIIa, in which R^1 is as described as above and R is chloro or fluoro, by a nucleophilic substitution reaction with a malonic acid ester or -half-ester in the presence of a base as described for example in *Org. Prep. Proc. Int.* 1990, *22*, 636-638, followed by the removal of one of the alkyl carboxylates via decarboxylation as described for example in *Synthesis* 1993, 51. The exact reaction conditions vary with the identity of the individual compounds and are described in the examples.

Scheme K



According to Scheme K, the dioxinones and ß-keto esters building blocks with the general formula IV and IVa can be prepared by methods known to someone skilled in the art from the corresponding carboxylic acid derivatives R^3-COR, i.e. free acids, methyl or ethyl esters and acid chlorides. The exact conditions for the corresponding compounds can be found in the experimental part.

The pharmaceutically acceptable salts can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I.

The compounds of formula I and their pharmaceutically acceptable salts are metabotropic glutamate receptor antagonists and can be used for the treatment or prevention of acute and/or chronic neurological disorders, such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are acute and chronic pain, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

The compounds of formula I and pharmaceutically acceptable salts thereof 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. However, the administration can 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 pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, 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.

As mentioned earlier, medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/ kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

The present invention relates also to the use of compounds of formula I and of pharmaceutically acceptable salts thereof for the production of medicaments, especially for the control or prevention of acute and/or chronic neurological disorders of the aforementioned kind.

The compounds of the present invention are group II mGlu receptor antagonists. The compounds show activities, as measured in the assay described below, of 10 μM or less, typically 1 μM or less, and ideally of 0.3 μM or less. In the table below are described some specific Ki values of preferred compounds.

Compound	K_i mGlu2 (μM)
4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.074
4-(8-morpholin-4-yl-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile	0.020
3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile	0.035
3-(8-iodo-4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile	0.075
3-[4-oxo-7-(3-phenyl-pyrrol-1-yl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile	0.075

Compound	K_i mGlu2 (μM)
4-(3-imidazol-1-yl-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.025
3-(8-methoxy-4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile	0.044
3-[7-(2-tert.-butyl-pyrrol-1-yl)-8-methoxy-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile	0.080
4-[3-(4-hydroxymethyl-thiazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.028
8-pyrrol-1-yl-4-(3-[1,2,3]triazol-1-yl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.0075
4-(3-oxazol-2-yl-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.023
5-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid ethyl ester	0.029
2-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid amide	0.062
2-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid (2-hydroxy-ethyl)-amide	0.091
4-[3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.006
4-(4-oxo-8-thiomorpholin-4-yl-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile	0.0009
7-ethoxy-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.0835
4-(8-ethoxy-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile	0.008

Compound	K_i mGlu2 (μM)
4-(8-methyl-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile	0.0085
2-[3-(3-methyl-isoxazol-5-yl)-phenyl]-4-oxo-8-thiomorpholin-4-yl-4,5-dihydro-3H-benzo[b][1,4]diazepine-7-carbonitrile	0.0325
7-chloro-4-[3-(5-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.0155
4-[3-(5-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.026
7-methyl-4-(3-pyrazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.070
4-[3-(2-hydroxymethyl-5-methyl-thiazol-4-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one	0.0065

[^{3}H]-LY354740 binding on mGlu2 transfected CHO cell membranes.

Transfection and cell culture

cDNA encoding the rat mGlu2 receptor protein in pBluescript II was obtained from Prof. S. Nakanishi (Kyoto, Japan), and subcloned into the eukaryotic expression vector pcDNA I-amp from Invitrogen (NV Leek, The Netherlands). This vector construct (pcD1mGR2) was co-transfected with a psvNeo plasmid encoding the gene for neomycin resistance, into CHO cells by a modified calcium phosphate method described by Chen & Okayama (1988). The cells were maintained in Dulbecco's Modified Eagle medium with reduced L-glutamine (2 mM final concentration) and 10 % dialysed foetal calf serum from Gibco BRL (Basel, Switzerland). Selection was made in the presence of G-418 (1000 ug/mL final). Clones were identified by reverse transcription of 5 μg total RNA, followed by PCR using mGlu2 receptor specific primers 5'-atcactgcttgggtttctggcactg-3' and 5'-agcatcactgtgggtggcataggagc-3' in 60 mM Tris HCl (pH 10), 15 mM $(NH4)_2SO_4$, 2 mM $MgCl_2$, 25 units/mL Taq Polymerase with 30 cycles annealing at 60 °C for 1 min., extention at 72 °C for 30 s, and 1 min. 95 °C denaturation.

Membrane preparation

Cells, cultured as above, were harvested and washed three times with cold PBS and frozen at –80 °C. The pellet was resuspended in cold 20 mM HEPES-NaOH buffer containing 10 mM EDTA (pH 7.4), and homogenised with a polytron (Kinematica, AG, Littau, Switzerland) for 10 s at 10 000 rpm. After centrifugation for 30 min. at 4 °C, the pellet was washed once with the same buffer, and once with cold 20 mM HEPES-NaOH buffer containing 0.1 mM EDTA, (pH 7.4). Protein content was measured using the Pierce method (Socochim, Lausanne, Switzerland) using bovine serum albumin as standard.

[^{3}H]-LY354740 binding

After thawing, the membranes were resuspended in cold 50mM Tris-HCl buffer containing 2 mM $MgCl_2$ and 2 mM $CaCl_2$, (pH 7) (binding buffer). The final concentration of the membranes in the assays was 25 µg protein/mL. Inhibition experiments were performed with membranes incubated with 10 nM [^{3}H]-LY354740 at room temperature, for 1 hour, in presence of various concentrations of the compound to be tested. Following the incubations, membranes were filtered onto Whatmann GF/C glass fiber filters and washed 5 times with cold binding buffer. Non specific binding was measured in the presence of 10 µM DCG IV. After transfer of the filters into plastic vials containing 10 mL of Ultima-gold scintillation fluid (Packard, Zürich, Switzerland), the radioactivity was measured by liquid scintillation in a Tri-Carb 2500 TR counter (Packard, Zürich, Switzerland).

Data analysis.

The inhibition curves were fitted with a four parameter logistic equation giving K_i values, and Hill coefficients.

EXAMPLES

General procedure A

Preparation of (2-nitro-phenyl)-carbamic acid tert.-butyl esters from 2-nitroanilines or 2-nitroacetanilides

Method a (from 2-nitroanilines): To a solution of diphosgene (4.1 mL, 34.1 mmol) in EtOAc (40 mL) at 0 °C was added a solution of the 2-nitroaniline (45.5 mmol) in EtOAc (200-500 mL), and the mixture was heated to reflux for 18 h. The solvent was removed in vacuum to leave a brown solid, which was triturated with hot hexane (200 mL). The solid material was filtered off and the filtrate was concentrated under reduced pressure to leave the pure 2-nitrophenylisocyanate as a yellow solid. This material was refluxed in a mixture of excess tert.-BuOH in CH_2Cl_2 for 2.5 h. Removal of the solvent left an orange solid which was purified by silica gel column chromatography with hexane/EtOAc to give the (2-nitro-phenyl)-carbamic acid tert.-butyl ester as a yellow solid.

Method b (from 2-nitroanilines): To a mixture of the 2-nitroaniline (142 mmol) and cesium carbonate (55.5 g, 170 mmol) in 2-butanone (740 mL) was dropwise added a solution of Boc_2O (37.8 g, 173 mmol) in 2-butanone (170 mL) and the resulting mixture was stirred at 50 °C to 80 °C until tlc indicated complete conversion. The solvent was removed in vacuum, the residue was treated with a mixture of H_2O (240 mL) and MeOH (240 mL) and extracted with hexane (3 x 500 mL). The combined hexane layer was washed with brine (200 mL) and all aqueous layers were reextracted with hexane (300 mL). All combined hexane layers were dried over $MgSO_4$, filtered and the solvent was removed in vacuum to give an orange solid, which was purified by silica gel column chromatography with hexane/EtOAc to give the (2-nitro-phenyl)-carbamic acid tert.-butyl ester as a yellow solid.

Method c (from 2-nitroanilines): To a solution of the 2-nitroaniline (550 mmol) and DMAP (1.22 g, 10 mmol) in THF (1000 mL) at 23 °C was dropwise added within 70 min a solution of Boc_2O (246 g, 1128 mmol) in THF (500 mL) and stirring was continued at 23 °C for 75 min. The entire mixture was evaporated to dryness and dried at HV to leave a dark brown solid. This material was dissolved in DCM (1100 mL), cooled to 0 °C and TFA (84 mL, 1100 mmol) was added dropwise. The mixture was stirred at 0 °C for 2 h, poured into icecold sat. $NaHCO_3$-sol., extracted with DCM, washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuum left a dark

brown solid which was coated on silica gel and purified by silica gel column chromatography with hexane/EtOAc to give the (2-nitro-phenyl)-carbamic acid tert.-butyl ester as a yellow solid.

Method d (from 2-nitroacetanilides): To a solution of the 2-nitroacetanilide (100 mmol) and DMAP (122 mg, 1 mmol) in THF (100 mL) at 23 °C was dropwise added within 15 min a solution of Boc_2O (22.92 g, 105 mmol) in THF (100 mL) and stirring was continued at 23 °C until tlc indicated completed conversion. The entire mixture was evaporated to dryness and dried at HV to leave a yellow to dark brown solid. This material was dissolved in THF (200 mL) and 25 % NH_4OH (77 mL, 500 mmol) was added dropwise. The mixture was stirred at 23 °C until tlc indicated complete conversion, poured into 1N HCl-sol., extracted with EtOAc, washed the organic layer with sat. $NaHCO_3$-sol. and brine, dried over MgSO4. Removal of the solvent in vacuum left an yellow to brown solid which was generally pure enough for further transformation or – if necessary - coated on silica gel and purified by silica gel column chromatography with hexane/EtOAc to give the (2-nitro-phenyl)-carbamic acid tert.-butyl ester as a yellow solid.

Example A1

(5-Fluoro-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared via the di-Boc-compound from 5-fluoro-2-nitro-4-trifluoromethyl-phenylamine [prepared from commercially available 4-amino-2-fluorobenzotrifluoride by: i.) acetylation withAc_2O in toluene at 23 °C; ii.) nitration with 100 % nitric acid from 10-23 °C; iii.) deacetylation with 2N NaOH in THF at 50 °C] (5.21 g, 23.2 mmol) and Boc_2O (10.63 g, 48.7 mmol), followed by treatment with 2 eq. TFA in CH_2Cl_2 according to the general procedure A (method c). Obtained as a light yellow solid (6.33 g, 84 %).

MS (ISN) 323 [$(M-H)^-$]; mp 104 °C.

Example A2

(2-Nitro-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared via the di-Boc-compound from 2-nitro-4-pyrrol-1-yl-phenylamine (Example F1) (13.5 g, 66.4 mmol) and Boc_2O (30.45 g, 139 mmol), followed by treatment with 2 eq. TFA in CH_2Cl_2 according to the general procedure A (method c). Obtained as a yellow solid (16.0 g, 79 %).

MS (ISN) 302 [$(M-H)^-$].

Example A3

[5-(2-Methoxy-ethoxy)-2-nitro-4-pyrrol-1-yl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from 5-(2-methoxy-ethoxy)-2-nitro-4-pyrrol-1-yl-phenylamine (Example D1) (711 mg, 2.6 mmol), Cs_2CO_3 (1.75 g, 5.4 mmol) and Boc_2O (1.12 g, 5.1 mmol) in 2-butanone (20 mL) at 80 °C for 3.5 h according to the general procedure A (method b). Obtained as a yellow solid (865 mg, 89 %).

MS (ISN) 376 [$(M-H)^-$]; mp 89-91 °C.

Example A4

(5-Methoxy-2-nitro-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared via the di-Boc-compound from 5-methoxy-2-nitro-4-pyrrol-1-yl-phenylamine (Example D2) (5.77 g, 24.7 mmol) and Boc_2O (11.1 g, 51 mmol), followed by treatment with 2 eq. TFA in CH_2Cl_2 according to the general procedure A (method c). Obtained as a yellow solid (5.56 g, 66 %).

MS (ISN) 332 [$(M-H)^-$].

Example A5

[4-(2-tert.-Butyl-pyrrol-1-yl)-5-methoxy-2-nitro-phenyl]-carbamic acid tert.-butyl ester

Obtained as side product in the preparation of Example A4 as a yellow solid (534 mg, 5.5 %).

MS (ISN) 388 [$(M-H)^-$].

Example A6

(5-Cyanomethyl-4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared via the isocyanate from (5-amino-2-iodo-4-nitro-phenyl)-acetonitrile [prepared from 5-chloro-2-nitro-phenylamine by: i.) iodination with ICl/NaOAc in HOAc at 60 °C; ii.) reaction with ethyl cyanoacetate and $KOBu^t$ in DMSO at 100 °C for 2h.; iii.) deacarboxylation with $LiCl/H_2O$ in DMSO at 120 °C for 2.5 h] (5.15 g, 17 mmol) and diphosgene (2.05 mL, 17 mmol) in EtOAc (150 mL), followed by treatment with tert.-BuOH (25 mL) in CH_2Cl_2 (25 mL) according to the general procedure A (method a). Obtained as a yellow solid (4.00 g).

MS (ISN) 402 [$(M-H)^-$]; mp 124-126 °C.

Example A7

(5-Methoxy-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared via the di-Boc-compound from 5-methoxy-2-nitro-4-trifluoromethyl-phenylamine (Example D3) (4.14 g, 17.5 mmol) and Boc_2O (8.04 g, 36.8 mmol), followed by treatment with 2 eq. TFA in CH_2Cl_2 according to the general procedure A (method c). Obtained as a yellow solid (5.86 g).

MS (ISN) 335 [$(M-H)^-$]; mp 68 °C.

Example A8

(5-Fluoro-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared via the di-Boc-compound from 5-fluoro-2-nitro-4-trifluoromethyl-phenylamine [prepared from 3-fluoro-4-(trifluoromethyl)-aniline [CAS-No. 69411-68-3] by the following sequence: i.) acetylation with Ac_2O in toluene at 23 °C; ii.) nitration 100% HNO_3 at 10 - 23 °C for 45 min; iii.) deacetylation with 2 N NaOH in THF at 50 °C for 6 h.] (5.21 g, 23.2 mmol) and Boc_2O (10.63 g, 48.7 mmol), followed by treatment with 2 eq. TFA in CH_2Cl_2 according to the general procedure A (method c). Obtained as a light yellow solid (6.33 g).

MS (ISN) 323 [$(M-H)^-$]; mp 104 °C.

Example A9

(5-Ethoxy-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared via the di-Boc-compound from 5-ethoxy-2-nitro-4-trifluoromethyl-phenylamine (Example D4) (4.16 g, 16.6 mmol).and Boc_2O (7.62 g, 34.9 mmol), followed by treatment with 2 eq. TFA in CH_2Cl_2 according to the general procedure A (method c). Obtained as a yellow solid (5.54 g).

MS (ISN) 349 [$(M-H)^-$]; mp 67 °C.

Example A10

(4-Cyano-5-fluoro-2-nitro-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared via the di-Boc compound from 4-cyano-5-fluoro-2-nitroaniline (24.9 g, 137 mmol) [Ohmori et al. J. Med. Chem. 1994,37, 467 – 475] and Boc_2O (61.5 g, 282 mmol), followed by treatment with 2 eq. TFA in CH_2Cl_2 according to the general procedure A (method c). Obtained by column chromatography (hexane/ethylacetate 4 : 1) as a light yellow solid (14.5 g, 39%).

MS (ISN) 280.1 [(M-H)$^-$].

Example A11

(5-Chloro-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared via the di-Boc-compound from commercially available 5-chloro-2-nitro-4-trifluoromethyl-phenylamine [CAS-No. 35375-74-7] (22.61 g, 94 mmol) and Boc_2O (42.06 g, 193 mmol), followed by treatment with 2 eq. TFA in CH_2Cl_2 according to the general procedure A (method c). Obtained as a yellow solid (31.82 g, 99 %).

MS (ISN) 339.1 [(M-H)$^-$] and 341 [(M+2-H)$^-$]; mp 113-115 °C.

General procedure B:

Preparation of 5-N-substituted-(2-nitro-phenyl)-carbamic acid tert.-butyl esters:

(5-Chloro or -fluoro-2-nitro-phenyl)-carbamic acid tert.-butyl ester was stirred with the desired amine optionally with DMSO, DMF, DMA, NMP or THF and/or DIPEA or Et_3N at temperatures from 23 °C to 130 °C until tlc indicated complete disappearance of the chloride or fluoride. The reaction was cooled to 23 °C poured into ice-water, the precipitate was filtered off, washed with water and dried in vacuum. In cases were the product did not precipitate, the mixture was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4. Filtration and removal of the solvent in vacuum left a crude product, which was – if necessary - purified by silica gel column chromatography with hexane/EtOAc to give the pure title compound.

Example B1

(5-Morpholin-4-yl-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (5-fluoro-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example A1) (1.62 g, 5.0 mmol) and morpholine (2.18 mL, 25.0 mmol) in DMSO (10 mL) at 23 °C according to the general procedure B. Obtained as a yellow solid (1.83 g).

MS (ISN) 390 [(M-H)$^-$]; mp 75 °C.

Example B2

(2-Amino-5-thiomorpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (5-fluoro-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example A1) (2.9 g, 8.94 mmol), Et_3N (5.6 mL, 40.23 mmol) and thiomorpholine (2.6 mL, 26.82 mmol) was stirred in DMSO (36 mL) at 23 °C according to the general procedure B. Obtained as a yellow solid (3.6 g).

MS (ISN) 406.4 [$(M-H)^-$]; mp 97-99 °C.

Example B3

(4-Cyano-5-morpholin-4-yl-2-nitro-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared from (4-cyano-5-fluoro-2-nitro-phenyl)-carbamic acid tert-butyl ester (Example A10) (4.67 g, 16.6 mmol) and morpholine (7.21 ml, 82.8 mmol) in DMSO (30 mL) at RT according to the general procedure B. Obtained as a yellow solid (5.01 g, 87%).

MS (ISP) 349.4 [$(M+H)^+$].

Example B4

(4-Cyano-2-nitro-5-thiomorpholin-4-yl-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared from (4-cyano-5-fluoro-2-nitro-phenyl)-carbamic acid tert-butyl ester (Example A10) (2.00 g, 7.11 mmol) and thiomorpholine (3.38 ml, 35.6 mmol) in DMSO (30 mL) at RT according to the general procedure C. Obtained as a light yellow solid (2.20 g, 85%).

MS (ISP) 363.1 [$(M-H)^-$].

Example B5

(5-Methyl-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester

To a suspension of (5-chloro-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example A11) (5.00 g, 14.7 mmol) and tetrakis(triphenylphosphine)-palladium in dioxane/water (9:1; 50 ml) was added at RT trimethylboroxine (2.04 ml, 14.7 mmol). The reaction mixture was stirred under reflux conditions for 15h, filtered,

evaporated and purified by column chromatography on silica gel (hexane/ethyl acetate 9:1) to yield a light yellow solid (3.25 g, 69%).

MS (ISP) 319.2 [(M-H)$^-$].

General procedure C:

Preparation of 5-S-substituted-(2-nitro-phenyl)-carbamic acid tert.-butyl esters:

To a solution of the thiol (2.2 mmol) in DMF was added NaOMe-sol. (5.4M in MeOH, 0.41 mL, 2.2 mmol) followed by the (5-chloro- or -fluoro-2-nitro-phenyl)-carbamic acid tert.-butyl ester (2.0 mmol) and stirring was continued at 23 °C until tlc indicated complete disappearance of the chloride or fluoride. Poured into ice-cold 5% citric acid, extracted with EtOAc, washed with sat. $NaHCO_3$-sol., brine, dried over $MgSO_4$. Removal of the solvent left an orange oil, which was purified by silica gel column chromatography with hexane/EtOAc to give the pure title compound.

General procedure D:

Preparation of 5-O-substituted-2-nitro-phenylamines:

To a suspension of KOH (85 %, 3.62-7.96 g, 55-121 mmol) in DMSO (50 mL) was added the alcohol (125-500 mmol) and the mixture was stirred at 23 °C until all KOH had dissolved. The 5-chloro-or-fluoro-2-nitro-phenylamine (50 mmol) was added in small portions and the resulting dark red clear solution was stirred at 23-60 °C until tlc indicated complete disappearance of the chloride or fluoride. Poured into ice-cold 1N HCl or ice-cold sat. NH_4Cl-sol., the precipitate was filtered off, washed with water and dried in vacuum. In cases were the product did not precipitate, the mixture was extracted with EtOAc, washed with 1N HCl or sat. NH_4Cl-sol. and brine, dried over $MgSO_4$. Removal of the solvent left a dark red solid, which was – if necessary - purified by silica gel column chromatography with hexane/EtOAc to give the pure title compound.

Example D1

5-(2-Methoxy-ethoxy)-2-nitro-4-pyrrol-1-yl-phenylamine

The title compound was prepared from 5-chloro-2-nitro-4-pyrrol-1-yl-phenylamine (Example F3) (1.01 g, 4 mmol), 2-methoxyethanol (1.58 mL, 20 mmol) and KOH (316 mg, 4.8 mmol) in DMSO (5 mL) according to the general procedure E. Obtained as an orange solid (870 mg).

MS (ISN) 276 [(M-H)$^-$]; mp 115-118 °C.

Example D2

5-Methoxy-2-nitro-4-pyrrol-1-yl-phenylamine

The title compound was prepared from 5-chloro-2-nitro-4-pyrrol-1-yl-phenylamine (Example F3) (5.94 g, 25 mmol), methanol (25 mL) and KOH (1.98 g, 30 mmol) in DMSO (25 mL) according to the general procedure E. Obtained as an orange solid (5.88 g).

MS (ISP) 234 [$(M+H)^+$].

Example D3

5-Methoxy-2-nitro-4-trifluoromethyl-phenylamine

The title compound was prepared from 5-chloro-2-nitro-4-trifluoromethyl-phenylamine [CAS-No. 35375-74-7] (4.61 g, 19.2 mmol) and KOH (2.78 g, 42.2 mmol) in MeOH (20 mL) and DMSO (40 mL) according to the general procedure E. Obtained as a yellow solid (4.18 g).

MS (ISN) 235 [$(M-H)^-$]; mp 56 °C.

Example D4

5-Ethoxy-2-nitro-4-trifluoromethyl-phenylamine

The title compound was prepared from 5-chloro-2-nitro-4-trifluoromethyl-phenylamine [CAS-No. 35375-74-7] (7.06 g, 29.3 mmol) and KOH (4.26 g, 64.6 mmol) in EtOH (30 mL) and DMSO (60 mL) according to the general procedure E. Obtained as a yellow solid (4.20 g).

MS (ISN) 249 [$(M-H)^-$]; mp 95 °C.

General procedure E:

Preparation of 2-nitro-5-pyrrol-1-yl-phenylamines:

Method a: A solution of the 5-chloro-or-fluoro-2nitro-phenylamine (10mmol), the pyrrole (40mmol) and KOH (85 %w/w, 990 mg, 15 mmol) in DMSO (8.6mL) was stirred for at 80 °C under argon atmosphere until tlc indicated complete conversion of the chloride or fluoride [cf. *J. Med. Chem.* 1994, *37*, 467]. Poured into ice-cold 1N HCl or ice-cold sat. NH_4Cl-sol., the precipitate was filtered off, washed with water and dried in vacuum. In cases were the product did not precipitate, the mixture was extracted with EtOAc, washed with 1N HCl or sat. NH_4Cl-sol. and brine, dried over $MgSO_4$. Removal of the solvent left a dark red solid, which was – if necessary - purified

by silica gel column chromatography with hexane/EtOAc to give the pure title compound.

Method b: To solution of the pyrrole (10 mmol) dry DMF (20 mL) at 0 °C was added NaH (60 % in mineral oil, 480 mg, 12 mmol) in 3 portions, followed by the 5-chloro- or fluoro-2-nitroaniline (10 mmol). The mixture was heated to 150 °C under argon atmosphere until tlc indicated complete conversion of the chloride or fluoride [cf. *J. Med. Chem.* 1992, *35*, 4455]. Poured into ice-cold 1N HCl or ice-cold sat. NH_4Cl-sol., the precipitate was filtered off, washed with water and dried in vacuum. In cases were the product did not precipitate, the mixture was extracted with EtOAc, washed with 1N HCl or sat. NH_4Cl-sol. and brine, dried over $MgSO_4$. Removal of the solvent left a dark red solid, which was – if necessary - purified by silica gel column chromatography with hexane/EtOAc to give the pure title compound.

Example E1

2-Nitro-5-pyrrol-1-yl-phenylamine

The title compound was prepared from 5-chloro-2nitroaniline (1.73 g, 10 mmol), pyrrole (2.8 mL, 40 mmol) and KOH (85 %, 990 mg, 15 mmol) in DMSO (8.6 mL) at 80 °C for 24 h according to the general procedure E (method a). Obtained as a brown solid (1.52 g).

MS (EI) 203 (M^+); mp >250 °C (dec.).

Example E2

1-(3-Amino-4-nitro-phenyl)-4-(2-chloro-phenyl)-1H-pyrrole-3-carbonitrile

The title compound was prepared from 5-chloro-2nitroaniline, 4-(o-Chlorophenyl)-pyrrole-3-carbonitrile [CAS-No. 74738-15-1] and NaH in DMF at 150 °C for 3 h according to the general procedure E (method b). Obtained as a yellow-brown solid (218 mg).

MS (ISN) 337 [$(M-H)^-$] and 339 [$(M+2-H)^-$]; mp 267-270 °C (dec.).

Example E3

1-(3-Amino-4-nitro-phenyl)-4-phenyl-1H-pyrrole-3-carbonitrile

Prepared from 5-chloro-2nitroaniline, 4-phenyl-pyrrole-3-carbonitrile [CAS-no. 40167-37-1] and NaH in DMF at 150 °C for 3 h according to the general procedure E (method b). Obtained as a dark red solid (168 mg).

MS (ISN) 303 [$(M-H)^-$]; mp 193-194 °C.

General procedure F:

Preparation of 2-nitro-4-(pyrrol-1-yl)-phenylamines or N-[5-(pyrrol-1-yl)-2-nitro-phenyl]-acetamides by condensation of 2-nitro-1,4-phenylenediamines or N-[5-amino-2-nitro-phenyl]-acetamides with 2,5-dimethoxytetrahydrofurans [cf. *J. Heterocycl. Chem.* 1988, *25*, 1003-1005]:

A mixture of the 2-nitro-1,4-phenylenediamine or N-[5-amino-2-nitro-phenyl]-acetamide (25 mmol), the 2,5-dimethoxytetrahydrofuran (26 - 32.5 mmol) in HOAc (7-150 mL) was stirred at 60-120 °C until tlc indicated complete conversion of the amine. After cooling to 23 °C, the mixture was poured into brine (500 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (300 mL) and dried over $MgSO_4$. Removal of the solvent left a brown residue, which was purified by silica gel column chromatography with cyclohexane/EtOAc to give the title compound.

The acidic or basic hydrolysis reactions from the N-[5-(pyrrol-1-yl)-2-nitro-phenyl]-acetamides to produce the 2-nitro-5-(pyrrol-1-yl)-phenylamines are described with the specific examples.

Example F1

2-Nitro-4-pyrrol-1-yl-phenylamine

The title compound was prepared from 2-nitro-1,4-phenylenediamine (20 g, 131 mmol), 2,5-dimethoxytetrahydrofuran (18.3 mL, 135 mmol) in HOAc (37 mL) at 95 °C for 3 h according to the general procedure F. Obtained as a red solid (13.5 g).

MS (EI) 203 (M^+).

Example F2

4-Iodo-2-nitro-5-pyrrol-1-yl-phenylamine

The title compound was prepared from N-(5-amino-4-iodo-2-nitro-phenyl)-acetamide (228 mg, 0.71 mmol)[prepared from commercially available 5-chloro-2-nitroaniline by the following sequence: i.) iodination with iodine monochloride, NaOAc in HOAc according to Wilson, J. Gerald; Hunt, Frederick C. *Aust. J. Chem.* 1983, *36*, 2317-25; ii.) nucleophilic aromatic substitution with NaN_3 in DMSO at 80 °C for 15 h; iii.) acetylation with AcCl in HOAc at 120 °C for 2 h according to *Eur. J. Med. Chem.* 1988, *23*, 553; iv.) Staudinger-reduction with PPh_3/H_2O in THF at 23 °C for 1 h] and 2,5-dimethoxytetrahydrofuran (0.14 mL, 1.08 mmol) in HOAc (10 mL) at 95 °C for 2 h according to the general procedure F. Obtained as a yellow solid (221 mg).

Deacetylation of this material (371 mg, 1.0 mmol) was perfomed by stirring with 1 N NaOH (2.0 mL, 2.0 mmol) in THF (3.4 mL) at 60 °C for 21 h. Obtained as a yellow solid (312 mg).

MS (ISN) 328 [(M-H)$^-$]; mp 150 °C.

Example F3

5-Chloro-2-nitro-4-pyrrol-1-yl-phenylamine

The title compound was prepared from 5-chloro-2-nitro-1,4-phenylenediamine[CAS-no. 26196-45-2] (4.69 g, 25 mmol), 2,5-dimethoxytetrahydrofuran (4.2 mL, 32.5 mmol) in HOAc (150 mL) at 95 °C for 2 h according to the general procedure F. Obtained as a red solid (4.10 g).

MS (ISN) 236 (M^+) and 238 [(M+2-H)$^-$].

Example F4

1-(3-Amino-4-nitro-phenyl)-1H-pyrrole-3-carbaldehyde

The title compound was prepared from 4-nitro-3-phenylendiamine and 2,5-dimethoxy-3-tetrahydrofuran-carboxaldehyde [CAS-no. 50634-05-4] in HOAc/toluene at 95 °C for 3 h according to the general procedure F. Obtained as an orange-brown solid (80 mg).

MS (EI) 231 (M^+).

Example F5

[1-(3-Amino-4-nitro-phenyl)-1H-pyrrol-3-yl]-methanol

The title compound was prepared from 1-(3-amino-4-nitro-phenyl)-1H-pyrrole-3-carbaldehyde (Example F4) by reduction with 2 eq. $NaBH_4$ in EtOH at 23 °C for 30 min. Obtained as a brown solid (20 mg).

MS (EI) 233 (M^+).

Example F6

2-Nitro-5-(3-phenyl-pyrrol-1-yl)-phenylamine

The title compound was prepared from N-(5-amino-2-nitro-phenyl)-acetamide [prepared from commercially available 5-chloro-2-nitroaniline by the following sequence: i.) nucleophilic aromatic substitution with NaN_3 in DMSO at 80 °C for 15 h; ii.) acetylation with AcCl in HOAc at 120 °C for 2 h according to *Eur. J. Med. Chem.* 1988, *23*, 553; iii.) Staudinger-reduction with PPh_3/H_2O in THF at 23 °C for 1 h] and

2,5-dimethoxy-3-phenyl-tetrahydro-furan [CAS-no. 207119-66-2] in HOAc at 60 °C for 2 days according to the general procedure F. Obtained as a brown solid (414 mg). Deacetylation of this material was perfomed by stirring with 25 % HCl in THF at 80 °C for 90 min. Obtained as a brown solid (179 mg).

MS (ISN) 278 [(M-H)$^-$].

Example F7

5-(3-Methoxymethyl-pyrrol-1-yl)-2-nitro-phenylamine

The title compound was prepared from N-(5-amino-2-nitro-phenyl)-acetamide [prepared from commercially available 5-chloro-2-nitroaniline as described in Example F6] and 2,5-dimethoxy-3-methoxymethyl-tetrahydro-furan [prepared from (2,5-dimethoxy-tetrahydro-furan-3-yl)-methanol [CAS-no. 207119-66-2] by methylation with 2.1 eq. NaH (95 %) and 5.5 eq. MeI in Et_2O at 0 °C for 2 h] in HOAc at 60 °C for 18 h according to the general procedure F. Obtained as a light yellow solid (86 mg). Deacetylation of this material was perfomed by stirring with 2 eq. 2 N NaOH-sol. in 1,4-dioxane at 60 °C for 2 h. Obtained as a yellow solid (69 mg).

MS (ISN) 246 [(M-H)$^-$].

Example F8

5-(2-Methoxymethyl-pyrrol-1-yl)-2-nitro-phenylamine

The title compound was prepared from N-(5-amino-2-nitro-phenyl)-acetamide [prepared from commercially available 5-chloro-2-nitroaniline as described in Example F6] and 2,5-dimethoxy-2-methoxymethyl-tetrahydro-furan [CAS-no. 98560-90-8] in HOAc at 60 °C for 2 h according to the general procedure F. Obtained as a light brown solid (620 mg). Deacetylation of this material was perfomed by stirring with 2 eq. 2 N NaOH-sol. in 1,4-dioxane at 60 °C for 21 h. Obtained as a yellow solid (511 mg).

MS (ISN) 246 [(M-H)$^-$].

Example F9

1-(3-Amino-4-nitro-phenyl)-1H-pyrrole-2-carboxylic acid methyl ester

The title compound was prepared from N-(5-amino-2-nitro-phenyl)-acetamide [prepared from commercially available 5-chloro-2-nitroaniline as described in Example F6] and 2,5-dimethoxy-tetrahydro-furan-2-carboxylic acid methyl ester [CAS-no. 39658-49-6] in HOAc at 60 °C for 2 h according to the general procedure F. Obtained as a light yellow solid (757 mg). Deacetylation of this material was perfomed

by stirring with 10 eq. NaOMe-sol. in MeOH at 23 °C for 1 h. Obtained as a yellow solid (594 mg).

MS (ISN) 260 [(M-H)$^-$]; mp 156-158 °C.

General procedure G:

Preparation of (5-hydroxy-2-nitro-phenyl)-carbamic acid tert.-butyl esters by deallylation of (5-allyloxy-2-nitro-phenyl)-carbamic acid tert.-butyl esters:

Method a: A mixture of the (5-allyloxy-2-nitro-phenyl)-carbamic acid tert.-butyl ester, $(PPh_3)_3RhCl$ (5 mol%) and DABCO (20 mol%) in EtOH was refluxed for 2.5 h according to *J. Org. Chem.* 1973, *38*, 3224. Added 5% citric acid, stirred at 23 °C for 15 min, extracted with EtOAc, washed with brine, dried over $MgSO_4$. Removal of the solvent left an orange solid, which was purified by silica gel column chromatography with hexane/EtOAc to give the title compound.

Method b: This method is also used for the deallylation of allylesters.

A mixture of the (5-allyloxy-2-nitro-phenyl)-carbamic acid tert.-butyl ester or allyl ester (10 mmol) and $(PPh_3)_4Pd$ (116 mg, 1 mol%) in THF (50 mL) was degassed for 10 min. Then morpholine (8.71 mL, 100 mmol) was added and the mixture was stirred at 0 °C to 23 °C until tlc indicated complete conversion of the allyl-compound (more $(PPh_3)_4Pd$ in portions of 0.5 mol% could be added in 24 h intervals to achieve complete conversion). Diluted with EtOAc, washed with 5% citric acid or 1 M HCl and brine, dried over $MgSO_4$. Removal of the solvent in vacuum left a solid, which was - if necessary - purified by silica gel column chromatography with hexane/EtOAc to give the title compound.

General procedure H:

Preparation of 5-O-substituted-(2-nitro-phenyl)-carbamic acid tert.-butyl esters from (5-hydroxy-2-nitro-phenyl)-carbamic acid tert.-butyl esters:

A mixture of the (5-hydroxy-2-nitro-phenyl)-carbamic acid tert.-butyl ester (10 mmol), $KHCO_3$ (1.30 g, 13 mmol) and the appropriate alkylating reagent (20 mmol) were stirred in DMF (20 mL) at 23 to 60 °C until tlc indicated complete conversion. Dilution with EtOAc was followed by aqueous workup with 5% citric acid, sat. $NaHCO_3$-sol., brine and drying over $MgSO_4$. Removal of the solvent left a crude material, which was purified by silica gel column chromatography with hexane/EtOAc to give the title compound.

General procedure I:

Preparation of (5-tert.-butoxycarbonylamino-4-nitro-phenyl)-acetic acid methyl esters and (5-cyanomethyl-4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl esters:

Step a: Nucleophilic aromatic substitution with malonic esters

To a solution of KOBut (0.56 g, 5.02 mmol) in DMSO (3 mL) was added dimethyl malonate (0.58 mL, 5.02 mmol) or ethyl cyanoacetate (0.54 mL, 5.02 mmol) followed by the (5-chloro-or -fluoro-2-nitro-phenyl)-carbamic acid tert.-butyl ester (2.51 mmol) and the resulting dark red clear solution was stirred at 100 °C until tlc indicated complete disappearance of the chloride or fluoride[cf. *Org. Prep. Proc. Int.* 1990, *22*, 636-638]. Poured into ice-cold 5% citric acid (100 mL), extracted with EtOAc (2 × 100 mL), washed with brine, dried over $MgSO_4$. Removal of the solvent left a yellow oil, which was purified by silica gel column chromatography with hexane/EtOAc to give the pure title compound as a yellow gum.

Step b: Decarboxylation reaction

A mixture of the above 2-(5-tert.-butoxycarbonylamino-4-nitro-phenyl)-malonic acid methyl ester (6.76 mmol), LiCl (573 mg, 13.52 mmol) and H_2O (0.122 mL, 6.76 mmol) in DMSO (46 mL) was stirred at 100 °C to 120 °C until tlc indicated complete decarboxylation [cf. *Synthesis* 1993, 51]. Poured into ice-water, extracted twice with EtOAc, washed with brine, dried over $MgSO_4$. Removal of the solvent left a yellow oil, which was purified by silica gel column chromatography with hexane/EtOAc to give the pure title compound as a yellow solid.

General procedure J:

Preparation of the (2-amino-phenyl)-carbamic acid tert.-butyl esters by reduction of (2-nitro-phenyl)-carbamic acid tert.-butyl esters:

Method a: Catalytic hydrogenation

A mixture of the nitro compound (1.0 mmol) in MeOH or EtOH and THF (1:1 ca. 20 mL) and 5-10% Palladium on carbon (20 mg) or Raney-Ni (20 mg) was stirred vigorously at 23 °C under hydrogen atmosphere until tlc indicated complete conversion. The catalyst was filtered off, washed thoroughly with MeOH or EtOH and THF (1:1), the solvent was removed in vacuum to give the title compound, which was generally pure enough for further transformations.

Method b: Reduction with $SnCl_2 \cdot 2H_2O$

A mixture of the nitro compound (1.0 mmol) and $SnCl_2 \cdot 2H_2O$ (5.0 mmol) was either stirred in EtOH (30 mL) at 70-80 °C or alternatively in pyridine (3 mL) and DMF (12 mL) at 23 °C under Argon atmosphere until tlc indicated complete conversion [cf. Tetr. Lett. 1984, 25, 839]. The reaction mixture was brought to pH 8 by addition of sat. $NaHCO_3$-sol. and extracted with EtOAc (2 × 100 mL). The combined organic layer were washed with brine and dried over Na_2SO_4. Removal of the solvent left a yellow solid, which - if necessary - can be purified by silica gel column chromatography.

Method c: Reduction with Zn and NH_4Cl

To a mixture of the nitro compound (1.0 mmol) in EtOH/THF/sat. NH_4Cl-sol. (1:1:1, 30 mL) was added Zinc dust (3.0 mmol) and the mixture was stirred at 70 °C under Argon atmosphere until tlc indicated complete conversion. Aqueous workup as described in method b.

Method d: Reduction with Fe and HOAc

To a mixture of the nitro compound (1.0 mmol) in THF/H_2O (4:1, 10-50 mL) was added Fe powder (6.0 mmol), followed by HOAc (10-12 drops) and the mixture was stirred at 70 °C under Argon atmosphere until tlc indicated complete conversion. Aqueous workup as described in method b.

Example J1

(2-Amino-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (5-morpholin-4-yl-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example B1) by hydrogenation with 10 % Pd/C according to the general procedure J (method a). Obtained as an amorphous red substance (1.72 g).

MS (ISP) 362 [$(M+H)^+$].

Example J2

(2-Amino-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (2-nitro-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example A2) by hydrogenation with 5 % Pd/C according to the general procedure J (method a). Obtained as a white solid (9.06 g).

MS (ISP) 274 [$(M+H)^+$].

Example J3

[2-Amino-5-(2-methoxy-ethoxy)-4-pyrrol-1-yl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from [5-(2-methoxy-ethoxy)-2-nitro-4-pyrrol-1-yl-phenyl]-carbamic acid tert.-butyl ester (Example A3) by hydrogenation with Raney-Nickel according to the general procedure J (method a). Obtained as an orange solid (196 mg).

MS (ISP) 348 [$(M+H)^+$]; mp 117-119 °C.

Example J4

(2-Amino-5-methoxy-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (5-methoxy-2-nitro-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example A4) (5.52 g, 16.6 mmol) by hydrogenation with 10% Pd/C according to the general procedure J (method a). Obtained as a light pink solid (4.1 g).

MS (ISP) 304 [$(M+H)^+$]; mp 134 °C.

Example J5

[2-Amino-4-(2-tert.-butyl-pyrrol-1-yl)-5-methoxy-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from [4-(2-tert.-butyl-pyrrol-1-yl)-5-methoxy-2-nitro-phenyl]-carbamic acid tert.-butyl ester (Example A5) (513 mg, 1.32 mmol) by hydrogenation with 10% Pd/C according to the general procedure J (method a). Obtained as a light brown gum (110 mg).

MS (ISP) 360 [$(M+H)^+$].

Example J6

(2-Amino-5-cyanomethyl-4-iodo-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (5-morpholin-4-yl-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example B1) (1.33 g, 3.3 mmol) by reduction with $SnCl_2 \cdot 2H_2O$ according to the general procedure J (method b). Obtained as a yellow solid (391 mg).

MS (EI) 373 (M^+); mp 152-154 °C.

Example J7

(2-Amino-5-thiomorpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (2-nitro-5-thiomorpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example B2) (1.2 g, 2.95 mmol) by reduction with $SnCl_2 \cdot 2H_2O$ according to the general procedure J (method b). Obtained as a yellow solid (978 mg).

MS (ISP) 378.3 [$(M+H)^+$]; mp 117-119 °C.

Example J8

[2-Amino-5-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from [5-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-2-nitro-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester [prepared from (2-amino-5-thiomorpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example B2) (2.4 g, 5.89 mmol) by oxidation with a 0.3M ammoniummolybdate solution (1.8 mL) and 30% H_2O_2 (13.6 mL) in acetone (14.7 mL) and H_2O (5.9 mL) from 0 °C to 23 °C for 1 h.] (2.4 g, 5.46 mmol) by reduction with $SnCl_2 \cdot 2H_2O$ according to the general procedure J (method b). Obtained as a yellow solid (2.15 g).

MS (ISP) 410.3 [$(M+H)^+$]; mp 161-164 °C.

Example J9

(2-Amino-5-methoxy-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (5-methoxy-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example A7) (5.79 g, 17.2 mmol) by hydrogenation with 10 % Pd/C according to the general procedure J (method a). Obtained as a yellow solid (5.36 g).

MS (ISP) 307 [$(M+H)^+$]; mp 125 °C.

Example J10

(2-Amino-5-fluoro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (5-fluoro-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example A8) (3.34 g, 10.3 mmol) by hydrogenation with 10 % Pd/C according to the general procedure J (method a). Obtained as a yellow solid (2.93 g).

MS (ISP) 295 [(M+H)$^+$]; mp 107-109 °C.

Example J11

(2-Amino-5-ethoxy-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (5-ethoxy-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example A9) (5.52 g, 15.8 mmol) by hydrogenation with 10 % Pd/C according to the general procedure J (method a). Obtained as a yellow solid (3.84 g).

MS (ISP) 321 [(M+H)$^+$]; mp 53 °C.

Example J12

(2-Amino-4-cyano-5-morpholin-4-yl-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared from (4-cyano-5-morpholin-4-yl-2-nitro-phenyl)-carbamic acid tert-butyl ester (Example B3) (5.01 g, 14.4 mmol) by reduction with $SnCl_2 \cdot 2H_2O$ according to the general procedure J (method b). Obtained as a pink solid (4.18 g, 91%).

MS (ISP) 319.4 [(M+H)$^+$]; mp 153 °C.

Example J13

(2-Amino-4-cyano-5-thiomorpholin-4-yl-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared from (4-cyano-2-nitro-5-thiomorpholin-4-yl-phenyl)-carbamic acid tert-butyl ester (Example B4) (2.08 g, 5.71 mmol) by reduction with $SnCl_2 \cdot 2H_2O$ according to the general procedure J (method b). Obtained as an off-white solid (1.83 g, 96%).

MS (ISP) 335.4 [(M+H)$^+$]; mp 169 °C.

Example J14

(2-Amino-5-chloro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared from (5-chloro-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example A11) (7.00 g, 20.5 mmol) by reduction with $SnCl_2 \cdot 2H_2O$ according to the general procedure J (method b). Obtained as a yellow solid (3.13 g, 49%).

MS (ISP) 309.3 [(M-H)$^-$]; mp 170 °C.

Example J15

(2-Amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared from (5-methyl-2-nitro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example B5) (3.40 g, 10.6 mmol) by hydrogenation with 10% Pd/C according to the general procedure J (method a). Obtained as light gray solid (3.0 g, 97%).

MS (ISP) 291.2 [$(M+H)^+$]; mp 174 °C.

The following examples relate to the preparation of the ethyl or tert.-butyl 3-aryl-3-oxo-propionates (general formula IVa), which serve as building blocks in the synthesis of the target compounds (Synthetic Scheme K):

General procedure K

Method a) Preparation of ethyl or tert.-butyl 3-aryl-3-oxo-propionates

The ethyl or tert.-butyl 3-aryl-3-oxo-propionates were prepared from the aryl acid chlorides and ethyl or tert.-butyl malonate potassium salt [CAS-no. 6148-64-7 and 75486-33-8] with Et_3N and $MgCl_2$ in CH_3CN at 0 °C to 23 °C according to *Synthesis* 1993, 290. If the free aryl carboxylic acid was employed in this reaction, it was activated by treatment with ethyl chloroformate and Et_3N in THF/CH_3CN at 0 °C prior to reaction with the malonate salt.

Method b) Preparation of tert.-butyl 3-aryl-3-oxo-propionates

The tert.-butyl 3-aryl-3-oxo-propionates were alternatively prepared from the methyl or ethyl aryl esters by treatment with lithium tert.-butyl acetate [prepared by treatment of tert.-butyl acetate with lithium diisopropylamide in THF at –78 °C] in the presence of lithium tert.-butoxide according to *Synthesis* 1985, 45. If the product contained residual starting material after workup, thus could be removed by selective saponification with LiOH in THF/MeOH/H_2O at 23 °C.

Method c) Preparation of 3-aryl-3-oxo-propionic acids

The 3-aryl-3-oxo-propionic acids were prepared from the aryl acid chlorides and bis(trimethylsilyl)malonate with Et_3N and LiBr in CH_3CN at 0 °C according to *Synth. Commun.* 1985, *15*, 1039 (method c1) or with n-BuLi in ether at –60 °C to 0 °C according to *Synthesis* 1979, 787 (method c2).

Example K1

3-Oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionic acid ethyl ester

The title compound was prepared from 3-[1,2,3]triazol-1-yl-benzoic acid, prepared by refluxing of methyl 3-azidobenzoate [CAS-No. 93066-93-4] in trimethylsilylacetylene, followed by saponification with aqueous NaOH in refluxing EtOH] by activation with ethyl chloroformate/Et_3N and reaction with ethyl malonate potassium salt with Et_3N and $MgCl_2$ in CH_3CN according to general procedure K (method a). Obtained as a light yellow solid (2.22 g).

MS (EI) 259 (M^+); mp 72-74 °C.

Example K2

3-(3-Cyano-phenyl)-3-oxo-propionic acid tert.-butyl ester

The title compound was prepared from methyl 3-cyanobenzoate [CAS-No. 13531-48-1] by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a light brown oily semisolid.

MS (EI) 245 (M^+).

Example K3

3-(2-Cyano-pyridin-4-yl)-3-oxo-propionic acid tert.-butyl ester

The title compound was prepared from 2-cyano-isonicotinic acid ethyl ester [CAS-No. 58481-14-4] by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a light brown solid (7.70 g).

MS (ISN) 245 [$(M-H)^-$].

Example K4

3-[3-(3-Methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionic acid tert.-butyl ester

The title compound was prepared from ethyl 3-(3-methyl-isoxazol-5-yl)-benzoate [prepared by reaction of ethyl 3-ethynylbenzoate [CAS-No. 178742-95-5] with a mixture of NCS, acetaldoxime, Et_3N and cat. amount of pyridine in $CHCl_3$ at 50 °C according to *Tetrahedron* 1984, *40*, 2985-2988] by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a yellow solid (2.54 g).

MS (ISP) 302 [$(M+H)^+$]; mp 50-56 °C.

Example K5

(RS)-3-Oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionic acid tert.-butyl ester

The title compound was prepared from (RS)-3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-benzoic acid methyl ester [prepared by the following sequence: i.) methyl 3-azidobenzoate [CAS-No. 93066-93-4] (15.55 g, 88 mmol) and (RS)-tert.-butyl-dimethyl-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-silane [CAS-No. 135294-85-8] (33.50 g, 132 mmol) were heated to 60 °C for 10 days; ii.) The obtained material (48.2 g, ca. 88 mmol) was stirred in TBAF (300 mL, 1M in THF) at 70 °C for 6 days and subsequently refluxed in 1N HCl (400 mL) for 2 h; iii.) The obtained material (16.15 g, 74 mmol) was stirred in MeOH (400 mL) and conc. H2SO4 (30 mL) at 23 °C for 11 days. iv.) Part of the obtained material (4.60 g, 19.7 mmol) was reacted with 3,4-dihydro-2H-pyran (2.67 mL, 29.5 mmol) and cat. amount p-TsOH·H_2O in DCM (38 mL) at 23 °C for 20 h.] (6.20 g, 19.5 mmol) by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a yellow oil (8.47 g).

MS (ISP) 402 [$(M+H)^+$].

Example K6

3-[2-(3-Methyl-isoxazol-5-yl)-pyridin-4-yl]-3-oxo-propionic acid tert.-butyl ester

The title compound was prepared from 2-(3-methyl-isoxazol-5-yl)-isonicotinic acid methyl ester [prepared by i.) reaction of 2-iodo-isonicotinic acid methyl ester [CAS-No. 134579-47-8] with trimethylsilylacetylene according to general procedure H; ii.) desilylation by reaction with cat. K_2CO_3 in MeOH at 0 °C for 4 h; iii.) cycloadditon with a mixture of NCS, acetaldoxime, Et_3N and cat. amount of pyridine in $CHCl_3$ at 50 °C according to *Tetrahedron* 1984, *40*, 2985-2988] by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a brown solid (5.17 g).

MS (EI) 302 (M^+); mp 59-67 °C.

Example K7

3-[3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-3-oxo-propionic acid tert.-butyl ester

The title compound was prepared from 3-(2-methyl-2H-pyrazol-3-yl)-benzoic acid methyl ester [prepared by i.) reaction of 1-(3-bromo-phenyl)-3-dimethylamino-propenone [CAS-No. 163852-04-8] with methylhydrazine in EtOH at 23 °C for 2.5 days; ii.) chromatographic separation of the obtained isomers; iii.) treatment of the

clean isomer with n-BuLi in THF at –78 °C for 1 h, followed by quenching with a stream of CO_2 and subsequent esterification with MeOH and conc. H_2SO_4 at 23 °C for 48 h.] by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a yellow oil (5.96 g).

MS (EI) 300 (M^+).

Example K8

3-[3-(5-Dimethylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-3-oxo-propionic acid tert.-butyl ester

The title compound was prepared from 3-(5-dimethylaminomethyl-[1,2,3]triazol-1-yl)-benzoic acid methyl ester [prepared from methyl 3-azidobenzoate following the synthetic steps i.) to iii.) as described in the preparation of Example K5 and reacting the obtained product with $SOCl_2$ in THF at 0 to 23 °C for 1 h, followed by addition of dimethylamine (7.9 M in H_2O) and stirring at 23 to 70 °C for1 h.] (2.14 g, 8.22 mmol) by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a yellow oil (2.90 g).

MS (ISP) 345 [$(M+H)^+$].

Example K9

3-[3-(3-Methoxymethyl-isoxazol-5-yl)-phenyl]-3-oxo-propionic acid tert.-butyl ester

The title compound was prepared from methyl 3-(3-methoxymethyl-isoxazol-5-yl)-benzoate [prepared by reaction of ethyl 3-ethynylbenzoate [CAS-No. 178742-95-5] with a mixture of NCS, 2-methoxyacetaldoxime [CAS-No. 71494-93-4], Et_3N and cat. amount of pyridine in $CHCl_3$ at 50 °C according to *Tetrahedron* 1984, *40*, 2985-2988] by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a light yellow liquid (1.548 g).

MS (EI) 331 (M^+).

Example K10

(RS)-3-Oxo-3-{3-[3-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-5-yl]-phenyl}-propionic acid tert.-butyl ester

The title compound was prepared from (RS)-3-[3-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-5-yl]-benzoic acid methyl ester [prepared by the following sequence: i.) 4-(3-bromo-phenyl)-2,4-dioxo-butyric acid ethyl ester [CAS-No. 151646-31-0] (7.55 g, 23 mmol) and hydroxylamine hydrochloride (4.74 g, 68 mmol) were refluxed in EtOH for 1 h; ii.) The obtained ester (5.94 g, 20 mmol) was reduced with $LiAlH_4$ (761 mg, 20

mmol) in THF at –10 °C for 1 h; iii.) The obtained alcohol (4.90 g, 19 mmol) was reacted with 3,4-dihydro-2H-pyran and cat. amount p-TsOH•H_2O in DCM at 23 °C for 20 h. iv.) The obtained THP-ether (5.24 g, 15 mmol) was treated with n-BuLi at –78 °C for 45 min, followed by a stream of CO_2. v.) The obtained crude acid was stirred in MeOH (90 mL) and conc. H_2SO_4 (6.5 mL) at 50 °C for 12 h. vi.) The obtained material (2.01 g, 8.62 mmol) was reacted with 3,4-dihydro-2H-pyran (1.17 mL, 12.9 mmol) and cat. amount p-TsOH•H_2O in DCM (17 mL) at 23 °C for 5 h.] (2.44 g, 7.7 mmol) by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a yellow oil (3.06 g).

MS (ISP) 402 [$(M+H)^+$].

Example K11

(RS)-3-Oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-3-yl]-phenyl}-propionic acid tert.-butyl ester

The title compound was prepared from (RS)-3-[5-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-3-yl]-benzoic acid methyl ester [prepared from (Z)-3-(hydroxyimino-methyl)-benzoic acid methyl ester [CAS-No. 91186-80-0] by treatment with NCS, cat. amount pyridine in $CHCl_3$ followed by addition of (RS)-tetrahydro-2-(2-propynyloxy)-2H-pyran and slow addition of Et_3N in $CHCl_3$ at 23 °C.] by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a yellow oil (3.00 g).

MS (ISN) 400.5 [$(M-H)^-$].

Example K12

3-Oxo-3-(3-pyrazol-1-yl-phenyl)-propionic acid tert.-butyl ester

The title compound was prepared from 3-pyrazol-1-yl-benzoic acid methyl ester [CAS-No. 168618-35-7] by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a yellow oil (5.00 g).

MS (EI) 286 (M^+).

Example K13

3-Oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionic acid tert.-butyl ester

The title compound was prepared from 3-[1,2,3]triazol-1-yl-benzoic acid [prepared by refluxing of methyl 3-azidobenzoate [CAS-No. 93066-93-4] in trimethylsilylacetylene, followed by saponification with aqueous NaOH in refluxing EtOH] (10.0 g, 52.86 mmol) by activation with ethyl chloroformate/Et_3N and reaction with mono tert.-butyl

malonate potassium salt with Et_3N and $MgCl_2$ in CH_3CN according to general procedure K (method a). Obtained as an orange oil (11.55 g).

MS (ISP) 288 [$(M+H)^+$].

Example K14

(RS)-3-Oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,4]triazol-1-yl]-phenyl}-propionic acid tert.-butyl ester

The title compound was prepared from (RS)-3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,4]triazol-1-yl]-benzoic acid methyl ester [prepared by the following sequence: i.) methyl 3-(1H-1,2,4-triazol-1-yl)-benzoate, [CAS-No. 167626-27-9] (39.4 g, 194 mmol) was heated in 36% formaldehyde-water (250 ml) in an autoclave for 41 h at 150 °C. Cristallisation from water and ethyl acetate/hexane (1:1) yielded a light brown solid (24.3 g, 54%) mp 164°C; ii.) The obtained material (24.3 g, 104 mmol) was reacted with 3,4-dihydro-2H-pyran (29.3 mL, 320 mmol) and cat. amount p-TsOH•H_2O in dichloromethane (360 mL)/ THF (300 ml) at 23 °C for 20 h. Purification by column chromatography on silica gel (toluene/ethyl acetate 1:1) gave a light brown oil.] (16.6 g, 52.3 mmol) by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as a light yellow oil (14.3 g, 68%).

MS (ISP) 400.4 [$(M-H)^-$].

Example K15

3-Oxo-3-(3-[1,2,4]triazol-1-yl-phenyl)-propionic acid tert-butyl ester

The title compound was prepared from methyl 3-[1,2,4]triazol-1-yl-benzoate [CAS-No. 167626-27-9] by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as an orange liquid (2.41 g).

MS (EI) 287 (M^+).

Example K16

3-(3-Imidazol-1-yl-phenyl)-3-oxo-propionic acid tert-butyl ester

The title compound was prepared from methyl 3-(1H-imidazol-1-yl)benzoate [prepared from 3-(1H-imidazol-1-yl)benzoic acid (*J. Med. Chem.* 1987, *30*, 1342; CAS-No. [108035-47-8] by refluxing in conc. H_2SO_4/MeOH] by treatment with lithium tert.-butyl acetate according to general procedure K (method b). Obtained as an orange-brown oil.

MS (ISP) 287 [$(M+H)^+$].

Example K17

3-Oxo-[3-[(5-methyl-oxazol-4-yl)-phenyl]-propionic acid tert.-butyl ester

a) Methyl 3-(2-bromo-propionyl)-benzoate

Bromine (4.6 ml) was dropped at 20-30 °C over 20 min. to a solution of methyl 3-propionyl-benzoate (17.24 g) in diethyl ether (0.15 L). Stirring was continued for 10 min. and the reaction mixture was then evaporated in vacuum to give methyl 3-(2-bromo-propionyl)-benzoate (25.5 g) as a yellow oil.

b) Methyl 3-[5-methyl-oxazol-4-yl]-benzoate

A mixture of methyl 3-(2-bromo-propionyl)-benzoate (5.42 g) and formamide (3.6 ml) was heated to 130°C for 5 h. The mixture was cooled and partitioned between H_2O and AcOEt. The organic layer was dried over Na_2SO_4 and evaporated and the residue was purified by chromatography on silica gel (AcOEt/hexane 1:4 as eluent) to give 1.8 g methyl 3-[5-methyl-oxazol-4-yl]-benzoate as white solid.

c) 3-([5-Methyl-oxazol-4-yl]- phenyl)-3-oxo-propionic acid tert.-butyl ester

Methyl 3-[5-methyl-oxazol-4-yl]-benzoate was treated with lithium tert.-butyl acetate according to the general procedure K (method b) to give 3-([5-methyl-oxazol-4-yl]-phenyl)-3-oxo-propionic acid tert.-butyl ester as a pale-yellow oil.

Example K18

a) Methyl 3-[2-hydroxymethyl-5-methyl-thiazol-4-yl]-benzoate

A solution of methyl 3-(2-bromo-propionyl)-benzoate (2.7 g) and 2-(tert.-butyl-carbonyloxy)thioacetamide (2.1 g) in EtOH (20 mL) was heated at reflux for 8 h. The mixture was partitioned between H_2O and AcOEt. The organic layer was dried and evaporated. The residue was dissolved in MeOH (20 ml), NaOMe (0.54 g) was added, and the mixture was heated to 60°C for 1 h. The mixture was diluted with AcOEt and then washed with 3N HCl and brine. The organic layer was dried and evaporated and the residue was crystallized from AcOEt to give methyl 3-[2-hydroxymethyl-5-methyl-thiazol-4-yl]-benzoate (1.17 g) as white solid.

b) Methyl 3-[5-methyl-2-(tetrahydro-pyran-2-yloxymethyl)-thiazol-4-yl]-benzoate

A mixture of the above material (1.1 g), dihydropyrane (0.73 mL) and p-toluenesulfonic acid hydrate (0.08 g) in AcOEt (10 mL) was stirred at 20 °C for 20 h. The solution was diluted with AcOEt, washed with 5% $NaHCO_3$ solution and with brine, dried and evaporated in vacuum. The residual oil was purified by chromatography on silica gel using AcOEt /hexane (1:3) as eluent to give methyl 3-[5-

methyl-2-(tetrahydro-pyran-2-yloxymethyl)-thiazol-4-yl]-benzoate (1.65 g) as a pale-yellow oil.

c) 3-Oxo-3-[3-[5-methyl-2-(tetrahydro-pyran-2-yloxymethyl)-thiazol-4-yl]-phenyl]-propionic acid tert.-butyl ester

The above material was treated with lithium tert.-butyl acetate according to general procedure K (method b) to give 3-oxo-3-[3-[5-methyl-2-(tetrahydro-pyran-2-yloxy-methyl)-thiazol-4-yl]-phenyl]-propionic acid tert.-butyl ester as a pale-yellow oil.

Example K19

3-Oxo-3-[3-[4-(tetrahydro-pyran-2-yloxymethyl)-thiazol-2-yl]-phenyl]-propionic acid tert-butyl ester

a) 3-(4-Hydroxymethyl-thiazol-2-yl)-benzoic acid methyl ester

A mixture of 3-thiocarbamoyl-benzoic acid methyl ester (7.8 g), 1,3-dichloro-2-propanone (8.4 g) and $NaHCO_3$ (8.4 g) in 1,4-dioxane (180 mL) was heated to 60 °C for 24 h. The reaction mixture was cooled to 20 °C and added to a stirred solution of NaOMe (5.4 g) in MeOH (200 mL). Stirring was continued for 0.5 h. The mixture was poured into ice-cold 2N HCl (200 mL) and the product was extracted with AcOEt. The organic layer was washed with brine, dried and evaporated in vacuum. The residue was crystallized from CH_2Cl_2 /hexane to give 3-(4-hydroxymethyl-thiazol-2-yl)-benzoic acid methyl ester (7.5 g) as light-brown crystals.

b) 3-[4-(Tetrahydro-pyran-2-yloxymethyl)-thiazol-2-yl]-benzoic acid methyl ester

A mixture of the above material (7.5 g), dihydropyrane (4.1 mL) and p-toluenesulfonic acid hydrate (0.19 g) in AcOEt (50 mL) was stirred at 20 °C for 1 h. The solution was diluted with AcOEt, washed with 5% $NaHCO_3$ solution and with brine, dried over Na_2SO_4 and evaporated in vacuum. The residual oil was purified by chromatography on silica gel using AcOEt/hexane (1:2) as eluent to give 3-[4-(tetrahydro-pyran-2-yloxymethyl)-thiazol-2-yl]-benzoic acid methyl ester (9.6 g) as a pale-yellow oil.

c) 3-Oxo-3-[3-[4-(tetrahydro-pyran-2-yloxymethyl)-thiazol-2-yl]-phenyl]-propionic acid tert-butyl ester

A sample of the above material (3.3 g) was treated with lithium tert.-butyl acetate according to general procedure K (method b) to give 3-oxo-3-[3-[4-(tetrahydro-pyran-2-yloxymethyl)-thiazol-2-yl]-phenyl]-propionic acid tert-butyl ester (3.25 g) as a pale-yellow oil.

MS (ISP) 418.2 [$(M+H)^+$].

The following examples relate to the preparation of the 6-aryl-2,2-dimethyl-[1,3]dioxin-4-ones (general formula IV), which serve as building blocks in the synthesis of the target compounds (Synthetic Scheme K):

General procedure L

Preparation of 6-aryl-2,2-dimethyl-[1,3]dioxin-4-ones

Method a)

The 6-aryl-2,2-dimethyl-[1,3]dioxin-4-ones were prepared from 3-aryl-3-oxo-propionic acids and catalytic amount of conc. H_2SO_4 or trifluoroacetic acid (TFA) in isopropenyl acetate at 23 °C according to *Chem. Pharm. Bull.* 1983, *31*, 1896. The final products were purified by silica gel column chromatography with hexane/EtOAc.

Method b)

The 6-aryl-2,2-dimethyl-[1,3]dioxin-4-ones were prepared from the tert.-butyl 3-aryl-3-oxo-propionates by treatment with trifluoroacetic anhydride (TFAA) in a mixture of TFA and acetone at 23 °C according to *Tetrahedron Lett.* 1998, *39*, 2253. The final products were if necessary purified by silica gel column chromatography with hexane/EtOAc.

Example L1

3-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile

The 3-(3-cyano-phenyl)-3-oxo-propionic acid was prepared from 3-cyanobenzoyl chloride (828 mg, 5 mmol) and bis(trimethylsilyl)malonate (2.56 mL, 10 mmol) with n-BuLi (1.6M in hexane, 6.25 mL) in ether at –60 °C to 0 °C according to general procedure K (method c2). The crude material (1.04 g) was transformed into the title compound by stirring in isopropenyl acetate and TFA according to general procedure L (method a). Obtained as a light yellow solid (0.8 g).

MS (EI) 229 (M^+); mp 138 °C (dec.).

Example L2

4-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-pyridine-2-carbonitrile

The title compound was prepared from 3-(2-cyano-pyridin-4-yl)-3-oxo-propionic acid tert.-butyl ester (Example M10) by stirring in TFA/acetone with TFAA according to general procedure L (method b). Obtained as a brown solid (3.30 g).

MS (EI) 230 (M^+); mp 132 °C (dec.).

Example L3

6-(3-Imidazol-1-yl-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one

The 3-(3-imidazol-1-yl-phenyl)-3-oxo-propionic acid was prepared from 3-(1H-imidazol-1-yl)benzoyl chloride hydrochloride [prepared by treatment of 3-(1H-imidazol-1-yl)-benzoic acid (*J. Med. Chem.* 1987, *30*, 1342; CAS-No. [108035-47-8] with $SOCl_2$) and bis(trimethylsilyl)malonate with Et_3N and LiBr in CH_3CN at 0 °C according to general procedure K (method c1). The crude material was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure L (method a). Obtained as an orange semisolid (617 mg).

MS (EI) 270 (M^+).

Example L4

6-(3-Iodo-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one.

The 3-(3-iodo-phenyl)-3-oxo-propionic acid was prepared from 3-iodobenzoyl chloride (21.0 g, 78.8 mmol) and bis(trimethylsilyl)malonate (21.0 mL, 82.8 mmol) with Et_3N (23 mL, 165.5 mmol) and LiBr (7.54 g, 86.7 mmol) in CH_3CN at 0 °C according to general procedure K (method c1). The crude material (21.9 g) was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure L (method a). Obtained as a yellow solid (9.6 g).

MS (EI) 330 (M^+); mp 79-80 °C (dec.).

Example L5

2,2-Dimethyl-6-(3-oxazol-2-yl-phenyl)-[1,3]dioxin-4-one

The 3-(3-oxazol-2-yl-phenyl)-3-oxo-propionic acid was prepared from 3-oxazol-2-yl-benzoyl chloride [prepared by the following sequence: i.) To a solution of isophthalic acid monomethyl ester (5.83 g) in DMF (150 mL) were added at –35 °C 88% 1-hydroxy-benzotriazole (7.83 g) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (9.78 g) and the mixture was stirred for 10 min. A solution of amino-acetaldehyde dimethylacetal (4.53 mL) in DMF (30 mL) was added dropwise over 10 min. The mixture was allowed to warm up to 0 °C over 2 h, diluted with H_2O and extracted with EtOAc. The organic layer was washed successively with 5% aqueous citric acid, sat. $NaHCO_3$-solution and brine, dried over Na_2SO_4 and evaporated in vacuum to give 3-[N-(2,2-dimethoxy-ethyl)-aminocarbonyl]-benzoic acid methyl ester (8.2 g) as an oil. ii.) To a solution of this material (5.4 g) in THF (40 mL) was added 6N HCl (10 mL). After being stirred 20 °C for 2 h, the mixture was

partitioned between EtOAc and brine. The organic layer was dried and evaporated to give 3-[N-(2-oxo-ethyl)-aminocarbonyl]-benzoic acid methyl ester (4.0 g) as an oil. iii.) A solution of this material (4.0 g) in dichloromethane (35 mL) was added at 20 °C to a solution of iodine (9.1 g) and triphenylphosphine (9.4 g) in dichloromethane (350 mL). The brown solution was stirred at 20 °C for 0.5 h and subsequently washed with 0.1M sodium thiosulfate solution and H_2O, dried over Na_2SO_4 and evaporated to give 3-oxazol-2-yl-benzoic acid methyl ester (1.05 g) as light-brown solid, mp. 64-70 °C. iv.) A mixture of this material (0.41 g), EtOH (4 mL) and 2N KOH (2 mL) was heated to 80 °C for 1.5 h. The solution was diluted with H_2O and washed with diethylether. The aqueous layer was acidified with 3N HCl and the product was extracted with EtOAc to give 3-oxazol-2-yl-benzoic acid (0.28 g) as a light-brown solid, mp. 187-188 °C. v.) This carboxylic acid (4.2 g) was heated with thionyl chloride in toluene and the resulting carboxylic acid chloride was used directly in the next step.] (4.4 g) and bis(trimethylsilyl)malonate with n-BuLi in ether at –60 °C to 0 °C according to general procedure K (method c2). The crude material was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure L (method a). Obtained as pale-yellow crystals (1.8 g).

MS (EI) 271 (M^+); mp 115-119 °C (dec.).

Example L6

5-[3-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-phenyl]-oxazole-4-carboxylic acid ethyl ester

The 5-(3-carboxyacetyl-phenyl)-oxazole-4-carboxylic acid ethyl ester was prepared from 5-(3-chlorocarbonyl-phenyl)-oxazole-4-carboxylic acid ethyl ester [prepared by the following sequence: i.) A mixture of isophthalic acid monoallyl ester (8.2 g), thionyl chloride (4.4 mL) and DMF (0.1 mL) in toluene (50 mL) was heated to 90 °C for 2 h. The mixture was evaporated in vacuum to give 3-chlorocarbonyl-benzoic acid allyl ester (9.0 g) as a light-yellow oil. ii.) To a solution of this material (9.0 g) and isocyano-acetic acid ethyl ester (4.4 mL) in THF (60 mL) was added at 0 °C Et_3N(14.0 mL). The mixture was stirred at 20 °C for 2.5 h and then evaporated in vacuum. The residue was partitioned between EtOAc and brine and the organic layer was dried and evaporated in vacuum. The residual oil was chromatographed on silica gel using EtOAc/hexane as eluent to give 5-(3-allyloxycarbonyl-phenyl)-oxazole-4-carboxylic acid ethyl ester (6.9 g) as a pale-yellow oil. iii.) This material (6.9 g) was subjected to the palladium-catalysed allylester cleavage according to general procedure G (method b) to give 5-(3-carboxy-phenyl)-oxazole-4-carboxylic acid ethyl ester (6.9 g) as light

brown crystals, mp 190-192 °C. iv.) This carboxylic acid (2.6 g) was heated with thionyl chloride in toluene and the resulting carboxylic acid chloride was used directly in the next step.] (2.8 g) and bis(trimethylsilyl)malonate with n-BuLi in ether at –60 °C to 0 °C according to general procedure K (method c2). The crude material was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure L (method a). Obtained as pale-yellow crystals (1.4 g).

MS (EI) 343 (M^+); mp 131-132 °C (dec.).

Example L7

2-[3-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-phenyl]-oxazole-4-carboxylic acid methyl ester

The 2-(3-carboxyacetyl-phenyl)-oxazole-4-carboxylic acid methyl ester was prepared from 2-(3-chlorocarbonyl-phenyl)-oxazole-4-carboxylic acid methyl ester [prepared by the following sequence: i.) To a solution of isophthalic acid (16.6 g) and 1,1,3,3-tetramethyl-guanidine (27.7 mL) in DMSO (75 mL) was added at 0 °C allyl bromide (18.6 mL) and the mixture was stirred at 20 °C for 6h. The mixture was diluted with EtOAc and washed with 2N HCl and brine. The organic layer was dried and evaporated. The remaining oil (21.5 g) was dissolved in DMSO (40 mL) and, after the addition of LiOH hydrate (2.8 g) and H_2O (1 mL), the mixture was heated to 60 °C for 3 h. The solution was diluted with EtOAc and then extracted with 5% $NaHCO_3$-solution. The aqueous layer was acidified with 25% HCl and the precipitated product was extracted with EtOAc to give isophthalic acid monoallyl ester (23.1 g) as white crystals. ii.) To a solution of this material (15.5 g) in DMF (350 mL) were added at –35 °C 88% 1-hydroxy-benzotriazole (15.4 g) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (19.2 g) and the mixture was stirred for 30 min. L-Serine methyl ester hydrochloride (14.0 g) was added at –50 °C followed by the addition of a solution of NEt_3 (12.5 mL) in DMF (50 mL) over 2 min. The mixture was allowed to warm up to 20 °C over 2 h and stirring was continued for 19 h. The mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed successively with 0.5 N HCl, sat. $NaHCO_3$-solution and brine, dried over Na_2SO_4 and evaporated in vacuum to give (S)-3-[N-(1-methoxycarbonyl-2-hydroxy)-aminocarbonyl]-benzoic acid allyl ester (20.6 g) as a crystallizing oil. iii.) To a solution of this material (20.6 g) in THF (0.4 L) was added methoxycarbonylsulfamoyl-triethylammonium hydroxide inner salt (17.6 g) and the mixture was stirred at 70 °C for 1 h. The mixture was evaporated in vacuum and the residue was purified by

chromatography using EtOAc/hexane (1:1) as eluent to give (S)-2-(3-allyloxycarbonyl-phenyl)-4,5-dihydro-oxazole-4-carboxylic acid methyl ester (16.7 g) as a yellow oil. iv.) To a solution of this material (14.7 g) in a mixture of acetonitrile (75 mL) and pyridine (75 mL) was added at 0 °C CCl_4 (14.4 mL) and subsequently DBU (15.0 mL). The mixture was stirred at 20 °C for 0.5 h, diluted with EtOAc and washed with 2N HCl and brine. The organic layer was dried and evaporated to give 2-(3-allyloxycarbonyl-phenyl)-oxazole-4-carboxylic acid methyl ester (10.1 g) as light-brown crystals, mp 104-107 °C. v.) This material (10.1 g) was subjected to the palladium-catalysed allylester cleavage according to general procedure G (method b) to give 2-(3-carboxy-phenyl)-oxazole-4-carboxylic acid methyl ester (7.0 g) as light-brown crystals, mp 209-210 °C (dec.). vi.) This carboxylic acid (1.26 g) was heated with thionyl chloride in toluene and the resulting carboxylic acid chloride was used directly in the next step.] (1.35 g) and bis(trimethylsilyl)malonate with n-BuLi in ether at –60 °C to 0 °C according to general procedure K (method c2). The crude material was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure L (method a). Obtained as pale-yellow crystals (1.4 g).

MS (EI) 329 (M^+); mp 141-142 °C (dec.).

Example L8

4-[3-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-phenyl]-thiazole-2-carboxylic acid ethyl ester

The 4-(3-carboxyacetyl-phenyl)-thiazole-2-carboxylic acid ethyl ester was prepared from 4-(3-chlorocarbonyl-phenyl)-thiazole-2-carboxylic acid ethyl ester [prepared by the following sequence: i.) A mixture of 3-(2-bromo-acetyl)-benzoic acid [CAS-no. 62423-73-8] (2.43 g) and ethyl thiooxamate [CAS-no. 16982-21-1] (1.6 g) in THF (40 mL) was heated to 60 °C for 4 h and then partitioned between EtOAc and brine. The organic layer was dried and evaporated and the residue was crystallized from EtOAc/hexane to give 4-(3-carboxy-phenyl)-thiazole-2-carboxylic acid ethyl ester (2.2 g) as off-white crystals, mp 225-228 °C. ii.) This carboxylic acid (2.1 g) was heated with thionyl chloride in toluene and the resulting carboxylic acid chloride was used directly in the next step.] (2.24 g) and bis(trimethylsilyl)malonate with n-BuLi in ether at –60 °C to 0 °C according to general procedure K (method c2). The crude material was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure L (method a). Obtained as yellow oil (2.7 g).

MS (EI) 359 (M^+).

Example I.9

2,2-Dimethyl-6-(3-[1,2,3]triazol-1-yl-phenyl)-[1,3]dioxin-4-one

The title compound was prepared from 3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionic acid tert.-butyl ester (Example K13) by stirring in TFA/acetone with TFAA according to general procedure L (method b). Obtained as a beige solid (7.80 g).

MS (EI) 271 (M^+); mp 144-147 °C (d...).

General procedure M:

Preparation of {2-[3-aryl-3-oxo-propionylamino]-phenyl}-carbamic acid tert.-butyl ester by reaction of (2-amino-phenyl)-carbamic acid tert.-butyl esters with ethyl or tert.-butyl 3-aryl-3-oxo-propionates or 6-aryl-2,2-dimethyl-[1,3]dioxin-4-ones:

A mixture of the (2-amino-phenyl)-carbamic acid tert.-butyl ester or (1.0-1.2 mmol) and (1.0-1.5 mmol) of the ethyl or tert.-butyl 3-aryl-3-oxo-propionate or 6-aryl-2,2-dimethyl-[1,3]dioxin-4-one was heated in toluene (4-8 mL) to 80 °C to 120 °C until tlc indicated complete consumption of the minor component. The solution was allowed to cool to 23 °C, whereupon the product generally crystallized (in cases where crystallization failed to appear it was induced by addition of hexane or ether, alternatively the reaction mixture was directly subjected to silica gel column chromatography). The solid was filtered off, washed with ether or mixtures of ether/hexane and dried in vacuum to give the {2-[3-aryl-3-oxo-propionylamino]-phenyl}-carbamic acid tert.-butyl esters, which was used directly in the following step or - if necessary - was purified by recrystallization or by silica gel column chromatography.

Example M1

(RS)-[5-Morpholin-4-yl-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J1) (181 mg, 0.5 mmol) and (RS)-3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionic acid tert-butyl ester (Example K5) (201 mg, 0.5 mmol) according to the general procedure M. Obtained as an amorphous off-white substance (223 mg).

MS (ISP) 689 [$(M+H)^+$].

Example M2

{2-[3-(2-Cyano-pyridin-4-yl)-3-oxo-propionylamino]-5-morpholin-4-yl-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J1) (181 mg, 0.5 mmol) and 3-(2-cyano-pyridin-4-yl)-3-oxo-propionic acid tert.-butyl ester (Example K3) (123 mg, 0.5 mmol) according to the general procedure M. Obtained as an off-white solid (137 mg).

MS (ISP) 534 [$(M+H)^+$]; mp 128 °C.

Example M3

{2-{3-[3-(3-Methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J1) (181 mg, 0.5 mmol) and 3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionic acid tert.-butyl ester (Example K4) (151 mg, 0.5 mmol) according to the general procedure M. Obtained as an amorphous yellow substance (117 mg).

MS (ISP) 589 [$(M+H)^+$].

Example M4

{3-(3-Cyano-phenyl)-N-(2-nitro-5-pyrrol-1-yl-phenyl)-3-oxo-propionamide

The title compound was prepared from 2-nitro-4-pyrrol-1-yl-phenylamine (Example E1) (203 mg, 1.0 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) (309 mg, 1.1 mmol) according to the general procedure M. Obtained as a brown solid (117 mg).

MS (ISN) 373 [$(M-H)^-$]; mp 206 °C (dec.).

Example M5

{2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4-pyrrol-1-yl-phenyl}-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example J2) (137 mg, 0.5 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) (115 mg, 0.5 mmol) according to the general procedure M. Obtained as a light red solid (139 mg).

MS (ISN) 443 [(M-H)$^-$].

Example M6

N-{5-[3-(2-Chloro-phenyl)-4-cyano-pyrrol-1-yl]-2-nitro-phenyl}-3-(3-cyano-phenyl)-3-oxo-propionamide

The title compound was prepared from 1-(3-amino-4-nitro-phenyl)-4-(2-chloro-phenyl)-1H-pyrrole-3-carbonitrile (Example E2) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) according to the general procedure M. Obtained as an orange-brown solid (203 mg).

MS (ISN) 508 [(M-H)$^-$] and 510 [(M+2-H)$^-$]; mp 229-232 °C.

Example M7

3-(3-Cyano-phenyl)-N-[5-(3-cyano-4-phenyl-pyrrol-1-yl)-2-nitro-phenyl]-3-oxo-propionamide

The title compound was prepared from 1-(3-amino-4-nitro-phenyl)-4-phenyl-1H-pyrrole-3-carbonitrile (Example E3) (254 mg, 0.835 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) (210 mg, 0.919 mmol) according to the general procedure M. Obtained as an orange solid (287 mg).

MS (ISN) 474 [(M-H)$^-$].

Example M8

3-(3-Iodo-phenyl)-N-(2-nitro-4-pyrrol-1-yl-phenyl)-3-oxo-propionamide

The title compound was prepared from 2-nitro-4-pyrrol-1-yl-phenylamine (Example E1) (610 mg, 3 mmol) and 6-(3-iodo-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one (Example L4) (1.49 g, 4.5 mmol) according to the general procedure M. Obtained as a brown solid (876 mg).

MS (ISN) 474 [(M-H)$^-$]; mp 193-196 °C.

Example M9

3-(3-Cyano-phenyl)-N-(4-iodo-2-nitro-5-pyrrol-1-yl-phenyl)-3-oxo-propionamide

The title compound was prepared from 4-iodo-2-nitro-5-pyrrol-1-yl-phenylamine (Example F2) (329 mg, 1.0 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) (252 mg, 1.1 mmol) according to the general procedure M. Obtained as a yellow solid (436 mg).

MS (EI) 500 (M^+); mp 183 °C.

Example M10

[2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-5-(2-methoxy-ethoxy)-4-pyrrol-1-yl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from [2-amino-5-(2-methoxy-ethoxy)-4-pyrrol-1-yl-phenyl]-carbamic acid tert.-butyl ester (Example J3) (186 mg, 0.54 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) (153 mg, 0.67 mmol) according to the general procedure M. Obtained as a beige solid (179 mg).

MS (EI) 518 (M^+); mp 102-130 °C.

Example M11

3-(3-Cyano-phenyl)-N-[5-(3-hydroxymethyl-pyrrol-1-yl)-2-nitro-phenyl]-3-oxo-propionamide

The title compound was prepared from [1-(3-amino-4-nitro-phenyl)-1H-pyrrol-3-yl]-methanol (Example F5) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) according to the general procedure M. Obtained as an orange solid (77 mg).

MS (ISN) 403 [$(M-H)^-$].

Example M12

3-(3-Cyano-phenyl)-N-[2-nitro-5-(3-phenyl-pyrrol-1-yl)-phenyl]-3-oxo-propionamide

The title compound was prepared from 2-nitro-5-(3-phenyl-pyrrol-1-yl)-phenylamine (Example F6) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) according to the general procedure M. Obtained as an orange solid (267 mg).

MS (ISN) 449 [$(M-H)^-$].

Example M13

3-(3-Cyano-phenyl)-N-[5-(3-methoxymethyl-pyrrol-1-yl)-2-nitro-phenyl]-3-oxo-propionamide

The title compound was prepared from 5-(3-methoxymethyl-pyrrol-1-yl)-2-nitro-phenylamine (Example F7) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) according to the general procedure M. Obtained as a yellow solid (102 mg).

MS (ISN) 417 [$(M-H)^-$].

Example M14

3-(3-Cyano-phenyl)-N-[5-(2-methoxymethyl-pyrrol-1-yl)-2-nitro-phenyl]-3-oxo-propionamide

The title compound was prepared from 5-(2-methoxymethyl-pyrrol-1-yl)-2-nitro-phenylamine (Example F8) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) according to the general procedure M. Obtained as a light brown solid (620 mg).

MS (ISN) 417 [(M-H)$^-$].

Example M15

1-{3-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4-nitro-phenyl}-1H-pyrrole-2-carboxylic acid methyl ester

The title compound was prepared from 1-(3-amino-4-nitro-phenyl)-1H-pyrrole-2-carboxylic acid methyl ester (Example F9) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) according to the general procedure M. Obtained as a yellow solid (840 mg).

MS (ISN) 431 [(M-H)$^-$]; mp 161-170 °C.

Example M16

3-(3-Imidazol-1-yl-phenyl)-N-(2-nitro-5-pyrrol-1-yl-phenyl)-3-oxo-propionamide

The title compound was prepared from 2-nitro-4-pyrrol-1-yl-phenylamine (Example E1) (163 mg, 0.8 mmol) and 6-(3-imidazol-1-yl-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one (Example L3) (261 mg, 1.0 mmol) according to the general procedure M. Obtained as a dark brown solid (249 mg).

MS (ISP) 416 [(M+H)$^+$].

Example M17

{2-[3-(3-Imidazol-1-yl-phenyl)-3-oxo-propionylamino]-4-pyrrol-1-yl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example J2) (1.37 g, 5.0 mmol) and 6-(3-imidazol-1-yl-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one (Example L3) (1.28 g, 4.75 mmol) according to the general procedure M. Obtained as a light brown foam (1.78 g).

MS (ISP) 486 [(M+H)$^+$].

Example M18

{2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-5-methoxy-4-pyrrol-1-yl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-methoxy-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example J4) (303 mg, 1.0 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) (252 mg, 1.1 mmol) according to the general procedure M. Obtained as an off-white solid (257 mg).

MS (ISP) 475 [$(M+H)^+$]; mp 190 °C.

Example M19

{4-(2-tert.-Butyl-pyrrol-1-yl)-2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-5-methoxy-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from [2-amino-4-(2-tert.-butyl-pyrrol-1-yl)-5-methoxy-phenyl]-carbamic acid tert.-butyl ester (Example J5) (89 mg, 0.25 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example L1) (63 mg, 0.275 mmol) according to the general procedure M. Obtained as an off-white solid (72 mg).

MS (ISP) 531 [$(M+H)^+$]; mp 172 °C.

Example M20

{2-[3-Oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionylamino]-4-pyrrol-1-yl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example J2) and 3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionic acid ethyl ester (Example K1) according to the general procedure M. Obtained as a light yellow solid (140 mg).

MS (ISP) 487 [$(M+H)^+$]; mp 81-84 °C.

Example M21

{5-Cyanomethyl-2-[3-(3-imidazol-1-yl-phenyl)-3-oxo-propionylamino]-4-iodo-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-cyanomethyl-4-iodo-phenyl)-carbamic acid tert.-butyl ester (Example J6) (363 mg, 0.973 mmol) and 6-(3-imidazol-1-yl-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one (Example L3) (411 mg, 1.52 mmol) according to the general procedure M. Obtained as a yellow oil (523 mg).

MS (ISP) 586.0 [$(M+H)^+$].

Example M22

(2-{3-[3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-3-oxo-propionylamino}-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J1) (181 mg, 0.5 mmol) and 3-[3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-oxo-propionic acid tert.-butyl ester (Example K7) (150 mg, 0.5 mmol) according to the general procedure M. Obtained as an amorphous yellow substance (114 mg).

MS (ISN) 586.0 [$(M-H)^-$].

Example M23

(RS)-[5-Morpholin-4-yl-2-(3-oxo-3-{3-[3-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-5-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J1) (181 mg, 0.5 mmol) and (RS)-3-oxo-3-{3-[3-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-5-yl]-phenyl}-propionic acid tert.-butyl ester (Example K10) (201 mg, 0.5 mmol) according to the general procedure M. Obtained as an amorphous yellow substance (57 mg).

MS (ISP) 689.0 [$(M+H)^+$].

Example M24

(2-{3-[3-(5-Dimethylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-3-oxo-propionylamino}-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J1) (181 mg, 0.5 mmol) and 3-[3-(5-dimethylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-3-oxo-propionic acid tert.-butyl ester (Example K8) (172 mg, 0.5 mmol) according to the general procedure M. Obtained as an amorphous yellow substance (179 mg).

MS (ISN) 630 [$(M-H)^-$].

Example M25

(2-{3-[3-(3-Methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-5-thiomorpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-thiomorpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J7) (189 mg, 0.5 mmol) and 3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionic acid tert.-butyl ester (Example K4) (170 mg, 0.56 mmol) according to the general procedure M. Obtained as a yellow solid (302 mg).

MS (ISN) 603.0 [$(M-H)^-$].

Example M26

{2-[3-(2-Cyano-pyridin-4-yl)-3-oxo-propionylamino]-5-thiomorpholin-4-yl-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-thiomorpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J7) (189 mg, 0.5 mmol) and 3-(2-cyano-pyridin-4-yl)-3-oxo-propionic acid tert.-butyl ester (Example K3) (150 mg, 0.61 mmol) according to the general procedure M. Obtained as a yellow solid (273 mg).

MS (ISN) 548.1 [$(M-H)^-$]; mp 53-55 °C.

Example M27

(RS)-[5-(1,1-Dioxo-1l 6-thiomorpholin-4-yl)-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from [2-amino-5-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester (Example J8) and (RS)-3-oxo-3-{3-[3-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-5-yl]-phenyl}-propionic acid tert.-butyl ester (Example K10) according to the general procedure M. Obtained as a light yellow foam (235 mg).

MS (ISP) 737.2 [$(M+H)^+$].

Example M28

{2-[3-(2-Cyano-pyridin-4-yl)-3-oxo-propionylamino]-5-methoxy-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-methoxy-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J9) (306 mg. 1.0 mmol) and 3-(2-cyano-pyridin-4-yl)-3-oxo-propionic acid tert.-butyl ester (Example K3) (246 mg, 1.0 mmol) according to the general procedure M. Obtained as a yellow solid (333 mg).

MS (ISP) 479 [$(M+H)^+$]; mp 92-119 °C.

Example M29

(5-Methoxy-2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-methoxy-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J9) (306 mg. 1.0 mmol) and 3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionic acid tert.-butyl ester (Example K4) (301 mg, 1.0 mmol) according to the general procedure M. Obtained as an off-white solid (301 mg).

MS (ISP) 534 [$(M+H)^+$]; mp 176 °C.

Example M30

(RS)-[5-Methoxy-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-methoxy-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J9) (306 mg. 1.0 mmol) and (RS)-3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionic acid tert.-butyl ester (Example K5) (401 mg, 1.0 mmol) according to the general procedure M. Obtained as an amorphous yellow substance (446 mg).

MS (ISN) 632 [$(M-H)^-$].

Example M31

(RS)-[5-Morpholin-4-yl-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-3-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J1) and (RS)-3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-3-yl]-phenyl}-propionic acid tert.-butyl ester (Example K11) according to the general procedure M. Obtained as a light yellow foam (774 mg).

MS (ISN) 687.2 [$(M-H)^-$].

Example M32

{5-Morpholin-4-yl-2-[3-oxo-3-(3-pyrazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J1) (361 mg, 1.0 mmol) and 3-oxo-3-(3-pyrazol-1-yl-phenyl)-propionic acid tert.-butyl ester (Example K12) (286 mg, 1.0 mmol) according to the general procedure M. Obtained as a light yellow amorphous substance (367 mg).

MS (ISN) 572 [$(M-H)^-$].

Example M33

{5-Morpholin-4-yl-2-[3-oxo-3-(3-[1,2,4]triazol-4-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J1) (434 mg, 1.2 mmol) and 3-oxo-3-(3-[1,2,4]triazol-4-yl-phenyl)-propionic acid ethyl ester [CAS-No. 335255-97-5] (259 mg, 1.0 mmol) according to the general procedure M. Obtained as an off-white solid (372 mg).

MS (ISP) 457.4 [$(M+H)^+$]; mp 151-160 °C.

Example M34

(RS)-[5-Fluoro-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-fluoro-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J10) (294 mg. 1.0 mmol) and (RS)-3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionic acid tert.-butyl ester (Example K5) (442 mg, 1.1 mmol) according to the general procedure M. Obtained as an orange solid (509 mg).

MS (ISN) 620.1 [(M-H)$^-$]; mp 42-45 °C.

Example M35

(RS)-[5-Ethoxy-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-ethoxy-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J11) (641 mg. 2.0 mmol) and (RS)-3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionic acid tert.-butyl ester (Example K5) (803 mg, 2.0 mmol) according to the general procedure M. Obtained as an amorphous yellow substance (916 mg).

MS (ISN) 646 [(M-H)$^-$].

Example M36

{2-[3-(2-Cyano-pyridin-4-yl)-3-oxo-propionylamino]-5-ethoxy-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-ethoxy-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J11) (160 mg. 0.5 mmol) and 3-(2-cyano-pyridin-4-yl)-3-oxo-propionic acid tert.-butyl ester (Example K3) (123 mg, 0.5 mmol) according to the general procedure M. Obtained as a yellow solid (159 mg).

MS (ISN) 491 [(M-H)$^-$]; mp 51 °C.

Example M37

{5-Ethoxy-2-[3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-ethoxy-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J11) (240 mg. 0.75 mmol) and 2,2-dimethyl-6-(3-[1,2,3]triazol-1-yl-phenyl)-[1,3]dioxin-4-one (Example L9) (215 mg, 0.75 mmol) according to the general procedure M. Obtained as an off-white solid (245 mg).

MS (ISN) 532 [(M-H)$^-$]; mp 175 °C.

Example M38

{5-Methoxy-2-[3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-methoxy-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J9) (306 mg. 1.0 mmol) and 2,2-dimethyl-6-(3-[1,2,3]triazol-1-yl-phenyl)-[1,3]dioxin-4-one (Example L9) (271 mg, 1.0 mmol) according to the general procedure M. Obtained as a yellow solid (394 mg).

MS (ISN) 518.1 [(M-H)$^-$].

Example M39

{2-[3-(2-Cyano-pyridin-4-yl)-3-oxo-propionylamino]-5-methyl-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester

The title compound was prepared from (2-amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example J15) and 3-(2-cyano-pyridin-4-yl)-3-oxo-propionic acid tert.-butyl ester (Example K3) according to the general procedure M. Obtained as a light yellow solid (250 mg).

MS (ISN) 461.2 [(M-H)$^-$]; mp 181 °C (dec.).

Example M40

{5-Cyano-2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-morpholin-4-yl-phenyl}-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-4-cyano-5-morpholin-4-yl-phenyl)-carbamic acid tert-butyl ester (Example J12) (318 mg, 1.0 mmol) and 3-(3-cyano-phenyl)-3-oxo-propionic acid tert-butyl ester (Example K2) (245 mg, 1.0 mmol) according to the general procedure M. Obtained as a light brown foam (290 mg, 59%).

MS (ISP) 490.3 [(M+H)$^+$].

Example M41

(RS)-[4-Cyano-5-morpholin-4-yl-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-phenyl]-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-4-cyano-5-morpholin-4-yl-phenyl)-carbamic acid tert-butyl ester (Example J12) (318 mg, 1.0 mmol) and (RS)-3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionic acid tert-butyl ester (Example K5) (402 mg, 1.0 mmol) according to the general procedure M. Obtained as a light brown foam (370 mg, 57%).

MS (ISP) 644.2 [(M-H)$^-$].

Example M42

(4-Cyano-2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-5-morpholin-4-yl-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-4-cyano-5-morpholin-4-yl-phenyl)-carbamic acid tert-butyl ester (Example J12) (318 mg, 1.0 mmol) and 3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo- propionic acid tert-butyl ester (Example K4) (301 mg, 1.0 mmol) according to the general procedure M. Obtained as a light brown foam (400 mg, 73%).

MS (ISP) 544.3 [(M-H)$^-$].

Example M43

(4-Cyano-2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-5-morpholin-4-yl-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-4-cyano-5-thiomorpholin-4-yl-phenyl)-carbamic acid tert-butyl ester (Example J13) (334 mg, 1.0 mmol) and 3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo- propionic acid tert-butyl ester (Example K4) (301 mg, 1.0 mmol) according to the general procedure M. Obtained as a light brown foam (440 mg, 78%).

MS (ISP) 562.3 [(M+H)$^+$].

Example M44

(RS)-[5-Chloro-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-chloro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J14) (774 mg, 2.49 mmol) and (RS)-3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionic acid tert-butyl ester (Example K5) (1.0 mg, 2.49 mmol) according to the general procedure M. Obtained as a light yellow foam (790 mg, 50%).

MS (ISP) 635.9 [(M-H)$^-$].

Example M45

(5-Chloro-2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-chloro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J14) (311 mg, 1.0 mmol) and 3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo- propionic acid tert-butyl ester (Example K4) (301 mg, 1.0 mmol) according to the general procedure M. Obtained as an off-white solid (210 mg, 39%).

MS (ISP) 536.1 [(M-H)$^-$]; mp 172°C.

Example M46

(RS)-[5-Methyl-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J15) (1.0 g, 3.44 mmol) and (RS)-3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionic acid tert-butyl ester (Example K5) (1.38 g, 3.44 mmol) according to the general procedure M. Obtained as an off-white foam (910 mg, 43%).

MS (ISP) 616.1 [(M-H)$^-$].

Example M47

{5-Methyl-2-[3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J15) (290 mg, 1.0 mmol) and 3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo- propionic acid tert-butyl ester (Example K4) (301 mg, 1.0 mmol) according to the general procedure M. Obtained as a white solid (240 mg, 46%).

MS (ISP) 516.2 [(M-H)$^-$].

Example M48

{5-Chloro-2-[3-oxo-3-(3-[1,2,4]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-chloro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J14) (311 mg, 1.0 mmol) and 3-oxo-3-(3-[1,2,4]triazol-1-yl-phenyl)-propionic acid tert-butyl ester (Example K15) (287 mg, 1.0 mmol) according to the general procedure M. Obtained as a white foam (360 mg, 69%).

MS (ISP) 522.0 [(M-H)$^-$].

Example M49

{5-Chloro-2-[3-(3-imidazol-1-yl-phenyl)-3-oxo-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-chloro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J14) (311 mg, 1.0 mmol) and 3-(3-imidazol-1-yl-phenyl)-3-oxo-propionic acid tert-butyl ester (Example K16) (286 mg, 1.0 mmol) according to the general procedure M. Obtained as a light yellow foam (160 mg, 31%).

MS (ISP) 521.0 [(M-H)$^-$].

Example M50

{5-Chloro-2-[3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-chloro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J14) (311 mg, 1.0 mmol) 3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionic acid ethyl ester (Example K1) (259 mg, 1.0 mmol) according to the general procedure M. Obtained as a light yellow oil (340 mg, 65%).

MS (ISP) 522.0 [(M-H)$^-$].

Example M51

{5-Methyl-2-[3-oxo-3-(3-[1,2,4]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J15) (290 mg, 1.0 mmol) and 3-oxo-3-(3-[1,2,4]triazol-1-yl-phenyl)-propionic acid tert-butyl ester (Example K15) (287 mg, 1.0 mmol) according to the general procedure M. Obtained as a white foam (420 mg, 83%).

MS (ISP) 502.1 [(M-H)$^-$].

Example M52

{5-Methyl-2-[3-(3-imidazol-1-yl-phenyl)-3-oxo-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J15) (290 mg, 1.0 mmol) and 3-(3-imidazol-1-yl-phenyl)-3-oxo-propionic acid tert-butyl ester (Example K16) (286 mg, 1.0 mmol) according to the general procedure M. Obtained as a light yellow foam (380 mg, 76%).

MS (ISP) 501.2 [(M-H)$^-$].

Example M53

{5-Methyl-2-[3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J15) (290 mg, 1.0 mmol) and 3-oxo-

3-(3-[1,2,3]triazol-1-yl-phenyl)-propionic acid ethyl ester (Example K1) (259 mg, 1.0 mmol) according to the general procedure M. Obtained as a light yellow oil (300 mg, 60%).

MS (ISP) 502.1 [(M-H)$^-$].

Example M54

{5-Methyl-2-[3-oxo-3-(3-pyrazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester

The title compound was prepared (2-amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J15) (290 mg, 1.0 mmol) and 3-oxo-3-(3-pyrazol-1-yl-phenyl)-propionic acid tert-butyl ester (Example K12) (286 mg, 1.0 mmol) according to the general procedure M. Obtained as a white solid (370 mg, 74%).

MS (ISP) 503.3 [(M+H)$^+$]; mp 172°C.

Example M55

(RS)-[5-Chloro-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,4]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert-butyl ester

The title compound was prepared from (2-amino-5-chloro-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J14) (900 mg, 2.90 mmol) and (RS)-3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,4]triazol-1-yl]-phenyl}-propionic acid tert-butyl ester (Example K14) (1.16 g, 2.90 mmol) according to the general procedure M. Obtained as a light yellow foam (790 mg, 43%).

MS (ISP) 635.3 [(M-H)$^-$].

General procedure N:

Preparation of 4-aryl-1,3-dihydro-benzo[b][1,4]diazepin-2-ones:

A solution or suspension of the {2-[3-aryl-3-oxo-propionylamino]-phenyl}-carbamic acid tert-butyl ester or {2-[3-aryl-3-oxo-propionylamino]-phenyl}-carbamic acid tert-butyl ester (1.0 mmol) in CH_2Cl_2 (5 mL) [anisole or 1,3-dimethoxybenzene (5-15 mmol) can be added if necessary] was treated with TFA (0.5-5.0 mL) at 0 °C and stirring was continued at 23 °C until tlc indicated complete consumption of the starting material.

Workup procedure a: The solvent was removed in vacuum, the residue treated with little ether, whereupon it crystallized. The solid was stirred with sat. $NaHCO_3$-sol. or 1M Na_2CO_3-sol., filtered, washed with H_2O and ether or mixtures of ether/THF/MeOH and was dried to give the title compound, which if necessary can be purified by crystallization from 1,4-dioxane or by silica gel column chromatography with cyclohexane/EtOAc or EtOAc/EtOH.

Workup procedure b: The reaction mixture was diluted with DCM or EtOAc, washed with sat. $NaHCO_3$-sol. or 1M Na_2CO_3-sol., brine and dried over $MgSO_4$ or Na_2SO_4. Removal of the solvent in vacuum left a material, which could be triturated with ether or mixtures of ether/THF/MeOH to give the title compound, or which if necessary can be purified by crystallization from 1,4-dioxane or by silica gel column chromatography with cyclohexane/EtOAc or EtOAc/EtOH.

Example 1

4-[3-(5-Hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (RS)-[5-morpholin-4-yl-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester (Example M1) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (51 mg).

MS (ISP) 487 [$(M+H)^+$]; mp 200 °C.

Example 2

4-(8-Morpholin-4-yl-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile

The title compound was prepared from {2-[3-(2-cyano-pyridin-4-yl)-3-oxo-propionylamino]-5-morpholin-4-yl-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester (Example M2) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (11 mg).

MS (ISP) 416 [$(M+H)^+$]; mp 220 °C.

Example 3

4-[3-(3-Methyl-isoxazol-5-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example M3) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (29 mg).

MS (ISP) 471 [$(M+H)^+$]; mp 170 °C.

Example 4

3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

The title compound was prepared from {2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-pyrrol-1-yl-phenyl}-carbamic acid tert-butyl ester (Example M5) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (1.51 g).

Alternatively, the title compound was also prepared from (3-(3-cyano-phenyl)-N-(2-nitro-5-pyrrol-1-yl-phenyl)-3-oxo-propionamide (Example M4) by reductive cyclization with $SnCl_2 \cdot 2H_2O$ in EtOH at 70 °C according to the general procedure J (method b). Obtained as an olive solid (161 mg).

MS (EI) 326 (M^+); mp 219 °C.

Example 5

4-(2-Chloro-phenyl)-1-[2-(3-cyano-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-7-yl]-1H-pyrrole-3-carbonitrile

The title compound was prepared from N-{5-[3-(2-chloro-phenyl)-4-cyano-pyrrol-1-yl]-2-nitro-phenyl}-3-(3-cyano-phenyl)-3-oxo-propionamide (Example M6) by reductive cyclization with Fe/HOAc in THF/H_2O at 80 °C according to the general procedure J (method d). Obtained as a brown solid (164 mg).

MS (EI) 461 (M^+) and 463 [$(M+2)^+$]; mp 252 °C (dec.).

Example 6

1-[2-(3-Cyano-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-7-yl]-4-phenyl-1H-pyrrole-3-carbonitrile

The title compound was prepared from 3-(3-cyano-phenyl)-N-[5-(3-cyano-4-phenyl-pyrrol-1-yl)-2-nitro-phenyl]-3-oxo-propionamide (Example M7) by reductive cyclization with Fe/HOAc in THF/H_2O at 80 °C according to the general procedure J (method d). Obtained as a brown solid (206 mg).

MS (EI) 427 (M^+); mp 274 °C (dec.).

Example 7

4-(3-Iodo-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from 3-(3-iodo-phenyl)-N-(2-nitro-4-pyrrol-1-yl-phenyl)-3-oxo-propionamide (Example M8) by reductive cyclization with $SnCl_2 \cdot 2H_2O$ in EtOH at 70 °C according to the general procedure J (method b). Obtained as an olive solid (624 mg).

MS (EI) 427 (M^+); mp 215-217 °C (dec.).

Example 8

3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzamide

A mixture of 4-(3-iodo-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 7) (214 mg, 0.5 mmol), $Pd(OAc)_2$ (4 mg, 3 mol%), PPh_3 (8mg, 8 mol%) and HDMS (0.52 mL, 2.5 mmol) in DMF (2 mL) was stirred under CO atmosphere at 60 °C for 4 h. The mixture was taken up in EtOAc, washed with 1 N HCl, sat. NaHCO3-sol. and brine, dried over MgSO4. Removal of the solvent in vacuum left a dark brown solid, which was purified by silica gel column chromatography with EtOAc/MeOH 95:5. Obtained as a yellow-brown solid (97 mg).

MS (EI) 344 (M^+); mp 238-239 °C (dec.).

Example 9

3-(8-Iodo-4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

The title compound was prepared from 3-(3-cyano-phenyl)-N-(4-iodo-2-nitro-5-pyrrol-1-yl-phenyl)-3-oxo-propionamide (Example M9) by reductive cyclization with $SnCl_2 \cdot 2H_2O$ in EtOH at 70 °C according to the general procedure J (method b). Obtained as a yellow solid (344 mg).

MS (EI) 452 (M^+); mp 215 °C.

Example 10

3-[8-(2-Methoxy-ethoxy)-4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

The title compound was prepared from [2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-5-(2-methoxy-ethoxy)-4-pyrrol-1-yl-phenyl]-carbamic acid tert.-butyl ester (Example M10) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a beige solid (22 mg).

MS (EI) 400 (M^+); mp 189-195 °C.

Example 11

3-[7-(3-Hydroxymethyl-pyrrol-1-yl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

The title compound was prepared from 3-(3-cyano-phenyl)-N-[5-(3-hydroxymethyl-pyrrol-1-yl)-2-nitro-phenyl]-3-oxo-propionamide (Example M11) by reductive cyclization with Fe/HOAc in THF/H_2O at 60 °C according to the general procedure J (method d). Obtained as a brown solid (18 mg).

MS (EI) 356 (M^+).

Example 12

3-[4-Oxo-7-(3-phenyl-pyrrol-1-yl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

The title compound was prepared from 3-(3-cyano-phenyl)-N-[2-nitro-5-(3-phenyl-pyrrol-1-yl)-phenyl]-3-oxo-propionamide (Example M12) by reductive cyclization with Fe/HOAc in THF/H_2O at 80 °C according to the general procedure J (method d). Obtained as a yellow solid (11 mg).

MS (EI) 402 (M^+).

Example 13

3-[7-(3-Methoxymethyl-pyrrol-1-yl)-4-oxo-4,5-dihydro-3H-benzo[b][1,5]diazepin-2-yl]-benzonitrile

The title compound was prepared from 3-(3-cyano-phenyl)-N-[5-(3-methoxymethyl-pyrrol-1-yl)-2-nitro-phenyl]-3-oxo-propionamide (Example M13) by reductive cyclization with Fe/HOAc in THF/H_2O at 80 °C according to the general procedure J (method d). Obtained as a brown solid (62 mg).

MS (EI) 370 (M^+).

Example 14

3-[7-(2-Methoxymethyl-pyrrol-1-yl)-4-oxo-4,5-dihydro-3H-benzo[b][1,5]diazepin-2-yl]-benzonitrile

The title compound was prepared from 3-(3-cyano-phenyl)-N-[5-(2-methoxymethyl-pyrrol-1-yl)-2-nitro-phenyl]-3-oxo-propionamide (Example M14) by reductive cyclization with Fe/HOAc in THF/H_2O at 80 °C according to the general procedure J (method d). Obtained as a brown solid (178 mg).

MS (EI) 370 (M^+); mp >197 °C (dec.).

Example 15

1-[2-(3-Cyano-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-7-yl]-1H-pyrrole-2-carboxylic acid methyl ester

The title compound was prepared from 1-{3-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-nitro-phenyl}-1H-pyrrole-2-carboxylic acid methyl ester (Example M15) by reductive cyclization with Fe/HOAc in THF/H_2O at 80 °C according to the general procedure J (method d). Obtained as a brown solid (323 mg).

MS (EI) 384 (M^+); mp >207 °C (dec.).

Example 16

4-(3-Imidazol-1-yl-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {2-[3-(3-imidazol-1-yl-phenyl)-3-oxo-propionylamino]-4-pyrrol-1-yl-phenyl}-carbamic acid tert.-butyl ester (Example M17) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (1.03 g).

Alternatively, the title compound was also prepared from 3-(3-imidazol-1-yl-phenyl)-N-(2-nitro-5-pyrrol-1-yl-phenyl)-3-oxo-propionamide (Example M16) by reductive cyclization with Fe/HOAc in THF/H_2O at 60 °C according to the general procedure J (method d). Obtained as a brown solid (100 mg).

MS (EI) 367 (M^+); mp 220 °C.

Example 17

3-(8-Methoxy-4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

The title compound was prepared from {2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-5-methoxy-4-pyrrol-1-yl-phenyl}-carbamic acid tert.-butyl ester (Example M18) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (10 mg).

MS (EI) 356 (M^+).

Example 18

3-[7-(2-tert.-Butyl-pyrrol-1-yl)-8-methoxy-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yll-benzonitrile

The title compound was prepared from {4-(2-tert.-butyl-pyrrol-1-yl)-2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-5-methoxy-phenyl}-carbamic acid tert.-butyl ester (Example M19) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (22 mg).

MS (EI) 412 (M^+); mp >250 °C.

Example 19

2-[3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-thiazole-4-carboxylic acid ethyl ester

A mixture of 3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-thiobenzamide [prepared from 3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile (Example 4) as follows: To a solution of hexamethyldisilthiane (1.38 mL, 6.5 mmol) in 1,3-dimethyl-2-imidazolidinone (6mL) was added at 23 °C sodium methoxide (0.34 g, 6.3 mmol). The mixture was stirred for 15 min. and the blue solution formed was then added to a solution of 3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile (Example 4) (0.98 g, 3 mmol) in 1,3-dimethyl-2-imidazolidinone (9 mL). The mixture was stirred for 3 h at 23 °C and then poured into H_2O (200 mL). The mixture was extracted with EtOAc, the organic layer was dried over Na_2SO_4 and evaporated in vacuum. The remaining oil was stirred for 0.5 h with H_2O (150 mL) and the precipitate formed was isolated by filtration and dried to give 3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-thiobenzamide (0.86 g) as light yellow solid, mp 198-201 °C (dec.), MS (ISN) 359.0 [$(M-H)^-$].] (0.3 g, 0.84 mmol) and ethyl bromopyruvate

(0.16 mL, 1.26 mmol) in ethanol (4 mL) was heated at reflux for 20 min. The solution was evaporated in vacuum and the residue was triturated with EtOAc to give the title compound (0.24 g) as a light-yellow solid.

MS (ISP) 455.2 [(M- H)$^-$]; mp 198-201 °C.

Example 20

4-[3-(4-Hydroxymethyl-thiazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

To a stirred suspension of 2-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-thiazole-4-carboxylic acid ethyl ester (Example 19) (0.34 g, 0.75 mmol) in THF (35 mL) was added at –20 °C over 40 min in 3 portions a 3.5 M solution of sodium dihydrido-bis(2-methoxyethoxy)aluminate in toluene (0.94 mL, 3.3 mmol). Stirring was continued at –20 °C for 20 min. and the reaction mixture was then poured into ice-cold 10% aqueous acetic acid. The product was extracted with EtOAc and the organic layer was washed successively with H_2O, sat. Na_2CO_3-solution and brine, dried over Na_2SO_4 and evaporated in vacuum. The residue was triturated with methanol to give the title compound (0.28 g) as light-yellow solid.

MS (ISN) 413.1 [(M-H)$^-$]; mp 238-240 °C.

Example 21

8-Pyrrol-1-yl-4-(3-[1,2,3]triazol-1-yl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {2-[3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionylamino]-4-pyrrol-1-yl-phenyl}-carbamic acid tert.-butyl ester (Example M20) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (36 mg).

MS (ISP) 369 [(M+H)$^+$]; mp 206-209 °C.

Example 22

4-(3-Oxazol-2-yl-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (2-amino-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example J2) (137 mg) and 2,2-dimethyl-6-(3-oxazol-2-yl-phenyl)-[1,3]dioxin-4-one (Example L5) (271 mg) according to the general procedure M. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (83 mg).

MS (ISP) 369.2 [(M+H)$^+$]; mp 251-253 °C.

Example 23

5-[3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid ethyl ester

The title compound was prepared from (2-amino-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example J2) (164 mg) and 5-[3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-phenyl]-oxazole-4-carboxylic acid ethyl ester (Example L6) (206 mg) according to the general procedure M. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (63 mg).

MS (ISP) 441.2 [(M+H)$^+$]; mp 222-224 °C.

Example 24

5-[3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid (2-hydroxy-ethyl)-amide

A solution of 5-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid ethyl ester (Example 23) (35mg) in 2-amino-ethanol (1 mL) was stirred at 50 °C for 4 h. The mixture was partitioned between H_2O and EtOAc. The organic layer was dried and evaporated in vacuum, and the residue was triturated with EtOAc to give the title compound (20 mg) as light-yellow solid.

MS (ISP) 456.4 [(M+H)$^+$]; mp 228-230 °C.

Example 25

2-[3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid methyl ester

The title compound was prepared from (2-amino-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example J2) (680 mg) and 2-[3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-phenyl]-oxazole-4-carboxylic acid methyl ester (Example L7) (820 mg) according to the general procedure M. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (770 mg).

MS (ISP) 433.2 [(M+H)$^+$]; mp 240-245 °C (dec.).

Example 26

4-[3-(4-Hydroxymethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

To a solution of 2-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid methyl ester (Example 25) (88 mg, 0.2 mmol) in THF (1.5 mL) were added successively MeOH (0.012 mL) and lithium borohydride (6.5 mg, 0.3 mmol). The mixture was stirred at 40 °C for 1 h and then partitioned between EtOAc and 1N HCl. The organic layer was washed with brine, dried and evaporated in vacuum. The residue was chromatographed on silica gel using EtOAc/hexane (1:2) as eluents to give the title compound (24 mg) as light-yellow solid.

MS (ISP) 399.4 [$(M+H)^+$]; mp 240-242 °C.

Example 27

2-[3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid amide

A suspension of 2-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid methyl ester (Example 25) (44mg) in a 5N solution (3 mL) of NH_3 in MeOH was stirred at 20 °C for 3 d. Insoluble material was filtered off and the solution was evaporated in vacuum. The residue was triturated with EtOAc to give the title compound (22 mg) as light-yellow solid.

MS (ISP) 412.2 [$(M+H)^+$]; mp 232-234 °C.

Example 28

4-[3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-thiazole-2-carboxylic acid ethyl ester

The title compound was prepared from (2-amino-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example J2) (1.9 g) and 5-[3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-phenyl]-thiazole-2-carboxylic acid ethyl ester (Example L8) (2.5 g) according to the general procedure M. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (0.85 g).

MS (ISP) 457.2 [$(M+H)^+$]; mp 213-215 °C.

Example 29

4-[3-(3-Methyl-isoxazol-5-yl)-phenyll-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (2-amino-4-pyrrol-1-yl-phenyl)-carbamic acid tert.-butyl ester (Example J2) (191 mg) and 3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionic acid tert.-butyl ester (Example K4) (211 mg) according to the general procedure M. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (92 mg).

MS (ISP) 383.2 [$(M+H)^+$]; mp 248-250 °C.

Example 30

4-[3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-thiazole-2-carboxylic acid amide

A sample of 4-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-thiazole-2-carboxylic acid ethyl ester (Example 28) (0.07 g) was reacted with ammonia in an analogous manner to the procedure described in Example 27 to give the title compound (0.05 g) as a light-yellow solid.

MS (ISP) 428.4[$(M+H)^+$]; mp 267-269 °C.

Example 31

2-[3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid bis-(2-hydroxy-ethyl)-amide

A solution of 2-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid methyl ester (Example 25)(88 mg) in 2-(2-hydroxy-ethylamino)-ethanol (2 mL) was stirred at 50 °C for 6 h. The mixture was partitioned between H_2O and EtOAc. The organic layer was dried and evaporated in vacuum, and the residue was triturated with EtOAc to give the title compound (32 mg) as light-yellow solid.

MS (ISP) 500.4 [$(M+H)^+$].

Example 32

4-[3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-thiazole-2-carboxylic acid (2-hydroxy-ethyl)-amide

A sample of 4-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-thiazole-2-carboxylic acid ethyl ester (Example 28) (0.26 g) was reacted with 2-amino-ethanol in an analogous manner to the procedure described in Example 34 to give the title compound (0.07 g) as a light-yellow solid.

MS (ISP) 472.3 [$(M+H)^+$]; mp 236-238 °C.

Example 33

4-[3-(2-Hydroxymethyl-thiazol-4-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

A sample of 4-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-thiazole-2-carboxylic acid ethyl ester (Example 28) (0.14 g) was reacted with sodium dihydrido-bis(2-methoxyethoxy)aluminat in an analogous manner to the procedure described in Example 20 to give the title compound (0.03 g) as an off-white solid.

MS (ISP) 415.2 [$(M+H)^+$]; mp 185-190 °C (dec.).

Example 34

2-[3-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid (2-hydroxy-ethyl)-amide

A solution of 2-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid methyl ester (Example 25) (88 mg) in 2-amino-ethanol (2 mL) was stirred at 50 °C for 2 h. The mixture was partitioned between EtOAc and H_2O, the organic layer was dried and evaporated in vacuum. The residue was chromatographed on silicag gel using EtOAc/hexane (1:1) as eluent and the purified product was triturated with Et_2O to give the title compound (20 mg) as light-yellow solid.

MS (ISP) 456.4 [$(M+H)^+$]; mp 242-244 °C.

Example 35

4-[3-(4-(Dimethylamino-methyl)-thiazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

A mixture of 4-[3-(4-(chloromethyl)-thiazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one {prepared as follows: A mixture of 3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-thiobenzamide [prepared as from 3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile (Example 4) as described in Example 19] (144 mg), 1,3-dichloro-2-propanone (76 mg) and sodium bicarbonate (50 mg) in 1,4-dioxane (3 mL) was heated to 60 °C for 15 h. The reaction mixture was cooled to 20 °C and diluted with H_2O (20 mL). The precipitate was collected and dried to give 4-[3-(4-(chloromethyl)-thiazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (154 mg) as a light-brown solid. MS (ISP) 427.4 [$(M+H)^+$].} (88 mg, 0.2 mmol) and potassium iodide (10 mg, 0.06 mmol) in a 33% solution of dimethylamine in methanol (1 mL, 5.5 mmol) was heated to 40 °C for 2 h. The mixture was evaporated in vacuum and the residue was chromatographed on silica gel using EtOAc/acetone (1:1) as eluent to give the title compound (31 mg) as a light-brown solid.

MS (ISP) 442.2 [$(M+H)^+$].

Example 36

4-[3-(4-Morpholin-4-ylmethyl-thiazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

A mixture of 4-[3-(4-(chloromethyl)-thiazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (cf. Example 35) (65 mg, 0.15 mmol), morpholine (0.11 mL, 1.2 mmol) and potassium iodide (5 mg, 0.03 mmol) in methanol (1 mL) was heated to 40 °C for 1 h. The mixture was diluted with H_2O and the precipitate formed was collected by filtration and chromatographed on silica gel using EtOAc/methanol (10:1) as eluent to give the title compound as a light-brown solid.

MS (ISP) 484.3 [$(M+H)^+$].

Example 37

[4-(3-Imidazol-1-yl-phenyl)-8-iodo-2-oxo-2,3-dihydro-1H-benzo[b][1,4]diazepin-7-yl]-acetonitrile

The title compound was prepared from {5-cyanomethyl-2-[3-(3-imidazol-1-yl-phenyl)-3-oxo-propionylamino]-4-iodo-phenyl}-carbamic acid tert.-butyl ester (Example M21) (520 mg, 0.89 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light pink solid (297 mg).

MS (EI) 467 (M^+); mp 243-245 °C.

Example 38

4-[3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (2-{3-[3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-oxo-propionylamino}-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example M22) (100 mg, 0.17 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (32 mg).

MS (ISP) 470 [$(M+H)^+$]; mp 211 °C.

Example 39

4-[3-(3-Hydroxymethyl-isoxazol-5-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (RS)-[5-morpholin-4-yl-2-(3-oxo-3-{3-[3-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-5-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester (Example M23) (57 mg, 0.08 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (11 mg).

MS (ISP) 487 [$(M+H)^+$]; mp 196 °C.

Example 40

4-[3-(5-Dimethylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (2-{3-[3-(5-dimethylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-3-oxo-propionylamino}-5-morpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example M24) (138 mg, 0.218

mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a beige solid (37 mg).

MS (ISP) 514 [$(M+H)^+$]; mp 180 °C.

Example 41

4-[3-(3-Methyl-isoxazol-5-yl)-phenyl]-7-thiomorpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-5-thiomorpholin-4-yl-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example M25) (310 mg, 0.5 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (80 mg).

MS (ISP) 487.2 [$(M+H)^+$]; mp 230-233 °C.

Example 42

4-(4-Oxo-8-thiomorpholin-4-yl-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile

The title compound was prepared from {2-[3-(2-cyano-pyridin-4-yl)-3-oxo-propionylamino]-5-thiomorpholin-4-yl-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester (Example M26) (265 mg, 0.5 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (111 mg).

MS (EI) 431.1 (M^+); mp 195-199 °C.

Example 43

7-(1,1-Dioxo-1l 6-thiomorpholin-4-yl)-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (RS)-[5-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester (Example M27) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (115 mg).

MS (ISP) 535.2 [$(M+H)^+$]; mp 216 °C (dec.).

Example 44

4-(8-Methoxy-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile

The title compound was prepared from {2-[3-(2-cyano-pyridin-4-yl)-3-oxo-propionylamino]-5-methoxy-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester (Example M28) (293 mg, 0.61 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (180 mg).

MS (EI) 360 (M^+); mp 227 °C.

Example 45

7-Methoxy-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (5-methoxy-2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-4-trifluoromethyl-phenyl)-carbamic acid tert.-butyl ester (Example M29) (254 mg, 0.48 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (96 mg).

MS (ISP) 416 [$(M+H)^+$]; mp 225 °C.

Example 46

4-[3-(5-Hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-7-methoxy-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (RS)-[5-methoxy-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester (Example M30) (404 mg, 0.64 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (134 mg).

MS (ISP) 432 [$(M+H)^+$]; mp 225 °C.

Example 47

7-Methoxy-4-[3-(5-pyrrolidin-1-ylmethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from 4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-7-methoxy-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 46) (86 mg, 0.2 mmol) by treatment with $SOCl_2$ (0.044 mL, 0.6 mmol) in CH_2Cl_2 (2 mL) from 23 °C to reflux for 15 min, followed by evaporation to dryness.

The crude chloride was dissolved in DMF (2 mL) and stirred with cat. amount of NaI and pyrrolidine (0.17 mL, 2.0 mmol) at 23 °C until tlc indicated complete conversion of the chloride. The reaction mixture was taken up in EtOAc, washed with water and brine, dried over Na_2SO_4. Removal of the solvent in vacuum left a yellow semisolid, which was purified by silica gel column chromatography. Obtained as a yellow solid (47 mg).

MS (ISP) 485 [$(M+H)^+$]; mp 215 °C.

Example 48

4-[3-(5-Hydroxymethyl-isoxazol-3-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (RS)-[5-morpholin-4-yl-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-isoxazol-3-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester (Example M31) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a white solid (386 mg).

MS (ISP) 467.3 [$(M+H)^+$]; mp 237-238 °C.

Example 49

7-Morpholin-4-yl-4-(3-pyrazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {5-morpholin-4-yl-2-[3-oxo-3-(3-pyrazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester (Example M32) (322 mg, 0.56 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (146 mg).

MS (ISP) 456 [$(M+H)^+$]; mp 166 °C.

Example 50

7-Morpholin-4-yl-4-(3-[1,2,4]triazol-4-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {5-morpholin-4-yl-2-[3-oxo-3-(3-[1,2,4]triazol-4-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester (Example M33) (360 mg, 0.627 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (176 mg).

MS (ISP) 457.4 [$(M+H)^+$]; mp 233-236 °C.

Example 51

7-Fluoro-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (RS)-[5-fluoro-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester (Example M34) (489 mg, 0.787 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (87 mg).

MS (ISN) 418.1 [$(M-H)^-$]; mp 197-199 °C.

Example 52

7-Ethoxy-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (RS)-[5-ethoxy-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert.-butyl ester (Example M35) (876 mg, 1.35 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (360 mg).

MS (ISP) 446 [$(M+H)^+$]; mp 214 °C.

Example 53

4-(8-Ethoxy-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile

The title compound was prepared from {2-[3-(2-cyano-pyridin-4-yl)-3-oxo-propionylamino]-5-ethoxy-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (Example M36) (133 mg, 0.27 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (28 mg).

MS (ISN) 373 [$(M-H)^-$]; mp 233 °C.

Example 54

4-[3-(5-Cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-7-ethoxy-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from 7-ethoxy-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 52) (134 mg, 0.3 mmol) by treatment with $SOCl_2$ (3 eq.)and cyclopropylamine (10 eq.) as described in Example 47. Obtained as a yellow solid (55 mg).

MS (ISN) 483 [$(M-H)^-$]; mp 80 °C.

Example 55

7-Ethoxy-4-{3-{5-[(2,2,2-trifluoro-ethylamino)-methyl]-[1,2,3]triazol-1-yl}-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from 7-ethoxy-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 52) (134 mg, 0.3 mmol) by treatment with $SOCl_2$ (3 eq.)and 2,2,2-trifluoroethylamine (20 eq.) as described in Example 47. Obtained as an off-white solid (57 mg).

MS (ISP) 527 [$(M+H)^+$]; mp 135 °C.

Example 56

7-Ethoxy-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {5-ethoxy-2-[3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester (Example M37) (203 mg, 0.38 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (148 mg).

MS (ISP) 416 [$(M+H)^+$]; mp 215 °C.

Example 57

7-Methoxy-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {5-methoxy-2-[3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester (Example M38) (394 mg, 0.758 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light brown solid (169 mg).

MS (ISN) 400.3 [$(M-H)^-$].

Example 58

4-(8-Methyl-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile

The title compound was prepared from {2-[3-(2-cyano-pyridin-4-yl)-3-oxo-propionylamino]-5-methyl-4-trifluoromethyl-phenyl}-carbamic acid tert.-butyl ester (Example M39) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (113 mg).

MS (ISN) 343.0 [$(M-H)^-$]; mp 235 °C.

Example 59

2-(3-Cyano-phenyl)-8-morpholin-4-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepine-7-carbonitrile

The title compound was prepared from {5-Cyano-2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-morpholin-4-yl-phenyl}-carbamic acid tert-butyl ester (Example M40) (0.28 g, 0.57 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (130 mg, 61%).

MS (ISP) 372.2 [$(M+H)^+$]; mp 259 °C.

Example 60

2-[3-(5-Hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-8-morpholin-4-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepine-7-carbonitrile

The title compound was prepared from (RS)-[4-cyano-5-morpholin-4-yl-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-phenyl]-carbamic acid tert-butyl ester (Example M41) (0.36 g, 0.56 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a yellow solid (152 mg, 61%).

MS (ISP) 444.3 [(M+H)$^+$]; mp 180 °C.

Example 61

2-[3-(3-Methyl-isoxazol-5-yl)-phenyl]-8-morpholin-4-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepine-7-carbonitrile

The title compound was prepared from (4-cyano-2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-5-morpholin-4-yl-phenyl)-carbamic acid tert-butyl ester (Example M42) (0.39 g, 0.71 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (215 mg, 70%).

MS (ISP) 428.5 [(M+H)$^+$]; mp 252 °C.

Example 62

2-[3-(3-Methyl-isoxazol-5-yl)-phenyl]-4-oxo-8-thiomorpholin-4-yl-4,5-dihydro-3H-benzo[b][1,4]diazepine-7-carbonitrile

The title compound was prepared from (4-cyano-2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-5-morpholin-4-yl-phenyl)-carbamic acid tert-butyl ester (Example M42) (0.43 g, 0.77 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (280 mg, 82%).

MS (ISP) 444.3 [(M+H)$^+$]; mp 245 °C.

Example 63

7-Chloro-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (RS)-[5-chloro-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert-butyl ester (Example M44) (0.79 g, 1.24 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (350 mg, 65%).

MS (ISP) 436.4 [(M+H)$^+$]; mp 198 °C.

Example 64

7-Chloro-4-[3-(5-hydroxymethyl-[1,2,4]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (RS)-[5-chloro-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,4]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert-butyl ester (Example M55) (0.78 g, 1.22

mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light brown solid (370 mg, 70%).

MS (ISP) 436.4 [$(M+H)^+$]; mp 212 °C.

Example 65

7-Chloro-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (5-chloro-2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example M45) (0.20 g, 0.37 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (131 mg, 84%).

MS (ISP) 418.1 [$(M-H)^-$]; mp 252 °C.

Example 66

7-Chloro-4-[3-(5-cyclopropylaminomethyl-[1,2,4]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from 7-chloro-4-[3-(5-hydroxymethyl-[1,2,4]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 63) (218 mg, 0.50 mmol) by reaction with thionylchloride in dichloromethane and subsequent treatment of the corresponding chloride with cyclopropylamine in DMF as described in Example 47. Obtained as an off-white solid (135 mg, 57%).

MS (ISP) 475.3 [$(M+H)^+$]; mp 191°C.

Example 67

7-Chloro-4-[3-(5-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from 7-chloro-4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 63) (218 mg, 0.50 mmol) by reaction with thionylchloride in dichloromethane and subsequent treatment of the corresponding chloride with cyclopropylamine in DMF as described in Example 47. Obtained as a light yellow solid (130 mg, 55%).

MS (ISP) 475.3 [$(M+H)^+$]; mp 206°C.

Example 68

4-[3-(5-Hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (RS)-[5-methyl-2-(3-oxo-3-{3-[5-(tetrahydro-pyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]-phenyl}-propionylamino)-4-trifluoromethyl-phenyl]-carbamic acid tert-butyl ester (Example M46) (0.90 g, 1.46 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (400 mg, 66%).

MS (ISP) 416.4 [$(M+H)^+$]; mp 215 °C.

Example 69

4-[3-(5-Cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from 4-[3-(5-hydroxymethyl-[1,2,3]triazol-1-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 68) (208 mg, 0.50 mmol) by reaction with thionylchloride in dichloromethane and subsequent treatment of the corresponding chloride with cyclopropylamine in DMF according to the method described in Example 47. Obtained as a light yellow solid (155 mg, 68%).

MS (ISP) 455.3 [$(M+H)^+$]; mp 181°C.

Example 70

7-Methyl-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from (5-methyl-2-{3-[3-(3-methyl-isoxazol-5-yl)-phenyl]-3-oxo-propionylamino}-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example M47) (0.23 g, 0.44 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (157 mg, 88%).

MS (ISP) 398.1 [$(M-H)^-$]; mp 240 °C.

Example 71

7-Chloro-4-(3-[1,2,4]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {5-chloro-2-[3-oxo-3-(3-[1,2,4]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (Example M48) (0.35 g, 0.67 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (211 mg, 78%).

MS (ISP) 406.4 [$(M+H)^+$]; mp 258 °C.

Example 72

7-Chloro-4-(3-imidazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {5-chloro-2-[3-(3-imidazol-1-yl-phenyl)-3-oxo-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (Example M49) (0.15 g, 0.29 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (55 mg, 47%).

MS (ISP) 405.4 [$(M+H)^+$]; mp 225 °C.

Example 73

7-Chloro-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {5-chloro-2-[3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (Example M50) (0.33 g, 0.63 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a light yellow solid (152 mg, 60%).

MS (ISP) 406.4 [$(M+H)^+$]; mp 219 °C.

Example 74

7-Methyl-4-(3-[1,2,4]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {5-methyl-2-[3-oxo-3-(3-[1,2,4]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (Example M51) (0.41 g, 0.81 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (255 mg, 81%).

MS (ISP) 386.3 [$(M+H)^+$]; mp 241 °C.

Example 75

4-(3-Imidazol-1-yl-phenyl)-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {2-[3-(3-imidazol-1-yl-phenyl)-5-methyl-3-oxo-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (Example M52) (0.37 g, 0.74 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (249 mg, 88%).

MS (ISP) 385.3 [$(M+H)^+$]; mp 212 °C.

Example 76

7-Methyl-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {5-methyl-2-[3-oxo-3-(3-[1,2,3]triazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (Example M53) (0.29 g, 0.58 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as an off-white solid (143 mg, 64%).

MS (ISP) 386.3 [$(M+H)^+$]; mp 237 °C.

Example 77

7-Methyl-4-(3-pyrazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

The title compound was prepared from {5-methyl-2-[3-oxo-3-(3-pyrazol-1-yl-phenyl)-propionylamino]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (Example M54) (0.36 g, 0.72 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure N. Obtained as a white solid (182 mg, 66%).

MS (ISP) 385.2 [$(M+H)^+$]; mp 235 °C.

Example 78

Acetic acid 2-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazol-4-ylmethyl ester

a) 4-[3-(4-Chloromethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

A suspension of 4-[3-(4-hydroxymethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 26) (1.0 g) in CH_2Cl_2 (15 mL) and thionyl chloride (0.27 mL) was heated with stirring to 40 °C for 0.5 h and subsequently

cooled in the ice bath. The solid was isolated by filtration and washed with CH_2Cl_2 to give 4-[3-(4-chloromethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (1.0 g) as yellow crystals.

b) Acetic acid 2-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazol-4-ylmethyl ester

A mixture of 4-[3-(4-chloromethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (146 mg), AcOK (52 mg) and KI (6 mg) in N,N-dimethylformamide (1 mL) was heated to 100 °C for 0.5 h. The mixture was cooled and diluted with H_2O. The precipitate formed was isolated by filtration and purified by chromatography on silica gel using AcOEt/CH_2Cl_2 (2:1,v/v) as eluent to give the title compound (45 mg) as yellow solid.

MS (ISP) 458.3 [$(M+NH4)^+$]; mp 206-207 °C.

Example 79

4-[3-(4-Methylaminomethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

A mixture of 4-[3-(4-chloromethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 78a) (125 mg) and potassium iodide (5 mg) in a 8M solution of methylamine in ethanol (1.5 mL) was stirred at 20 °C for 16 h. H_2O (20 mL) was added and the precipitated collected by filtration and purified by chromatography on silica gel using MeOH as eluent. The product was stirred with 20% aqueous MeOH (10 mL) the pH of the mixture being set to 11 by addition of 1N NaOH solution, and the solid was isolated by filtration to give the title compound (54 mg) as yellow solid.

MS (ISP) 412.3 [$(M+H)^+$]; mp 182-183 °C.

Example 80

4-[3-(4-Dimethylaminomethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

A mixture of 4-[3-(4-chloromethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 78a) (125 mg) and KI (5 mg) in a 5.6M solution of dimethylamine in EtOH (1.5 mL) was stirred at 20 °C for 16 h. H_2O (20 mL) was added and the precipitate was collected by filtration and purified by chromatography on silica gel using MeOH as eluent. The product was stirred with 20% aqueous MeOH (10 mL) the pH of the mixture being set to 11 by addition of 1N

NaOH solution, and the solid was isolated by filtration to give the title compound (50 mg) as yellow solid.

MS (ISP) 426.5 [$(M+H)^+$]; mp 172-175 °C.

Example 81

4-[3-(4-Morpholin-4-ylmethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

A mixture of 4-[3-(4-chloromethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 78a) (125 mg), morpholine (0.25 mL) and KI (5 mg) in EtOH (1 mL) was stirred at 60 °C for 2 h. in H_2O (20 mL) was added to the cooled solution and the precipitate was collected by filtration and purified by chromatography on silica gel using MeOH as eluent. The product was stirred with 20% aqueous MeOH(10 mL) the pH of the mixture being set to 11 by addition of 1N NaOH solution, and the solid was subsequently isolated by filtration to give the title compound (60 mg) as yellow solid.

MS (ISP) 468.3 [$(M+H)^+$]; mp. 166-167 °C.

Example 82

4-(4-Oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile

A mixture of of (2-amino-4-pyrrol-1-yl-phenyl)-carbamic acid tert-butyl ester (Example J2) (0.14 g) and 3-(2-cyano-pyridin-4-yl)-3-oxo-propionic acid tert-butyl ester (Example K3) (0.14 g) in toluene (1.5 mL) was heated to 100 °C for 4 h, a fine precipitate being formed. The mixture was cooled and the precipitae was isolated by filtration. A solution of this solid in CH_2Cl_2 (2.5 mL) and TFA (2.5 mL) was stirred for 0.5 h at 20 °C and then evaporated in vacuum. The residual oil was dissolved in AcOEt and the solution was washed with saturated Na_2CO_3 solution and with brine, dried over Na_2SO_4 and evaporated in vacuum. The solid residue was triturated with CH_2Cl_2 to give the title compound (0.06 g) as light-yellow crystals.

MS (ISN) 325.8 [$(M-H)^-$]; mp 243-244 °C.

Example 83

7-Methyl-4-[3-(5-methyl-oxazol-4-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

A mixture of (2-amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J15) (0.145 g) and 3-oxo-[3-[(5-methyl-oxazol-4-yl)- phenyl]-propionic acid tert.-butyl ester (Example K17) (0.26 g) in toluene (1.5 mL) was heated to 100 °C for 8 h. The mixture was cooled and evaporated in vacuum. A solution of the residue in a mixture of CH_2Cl_2 (2.5 mL) and TFA (2.5 mL) was stirred for 0.5 h at 20 °C. The mixture was evaporated in vacuum, the residual oil was dissolved in AcOEt and the solution was washed with saturated $NaHCO_3$ solution and with brine, dried over Na_2SO_4 and evaporated in vacuum. The residue was crystallized from CH_2Cl_2 to give the title compound (0.12 g) as white crystals.

MS (ISP) 444.0 [$(M+H)^+$]; mp. 241-242 °C.

Example 84

4-[3-(2-Hydroxymethyl-5-methyl-thiazol-4-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

A mixture of (2-amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J15) (0.145 g) and 3-[3-[5-methyl-2-(tetrahydro-pyran-2-yloxymethyl)-thiazol-4-yl]-phenyl]-3-oxo-propionic acid tert.-butyl ester (Example K18) (0.18 g) in toluene (1.5 mL) was heated to 100 °C for 8 h. The mixture was cooled and evaporated in vacuum. A solution of the residue in a mixture of CH_2Cl_2 (2.5 mL) and trifluoroacetic acid (2.5 mL) was stirred for 0.5 h at 20 °C. The mixture was evaporated in vacuum, the residual oil was dissolved in AcOEt and the solution was washed with saturated $NaHCO_3$ solution and with brine, dried over Na_2SO_4 and evaporated in vacuum. The residue was triturated with CH_2Cl_2 to give the title compound (0.07 g) as white crystals.

MS (ISN) 444.0 [$(M-H)^-$]; mp 214-217 °C.

Example 85

4-[3-(4-Hydroxymethyl-thiazol-2-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

A mixture of (2-amino-5-methyl-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (Example J15) (0.145 g) and 3-oxo-3-[3-[4-(tetrahydro-pyran-2-yloxymethyl)-thiazol-2-yl]-phenyl]- propionic acid tert.-butyl ester (Example K19) (0.23 g) in

toluene (2 mL) was heated to 100 °C for 5 h. The mixture was cooled and evaporated in vacuum. A solution of the residue in a mixture of CH_2Cl_2 (2 mL) and TFA (2 mL) was stirred for 0.5 h at 20 °C. The mixture was evaporated in vacuum, the residual oil was dissolved in AcOEt and the solution was washed with saturated $NaHCO_3$ solution and with brine, dried over Na_2SO_4 and evaporated in vacuum. The residue was crystallized from CH_2Cl_2 /hexane to give the title compound (0.04 g) as light-brown crystals.

MS (ISP) 430.0 [$(M-H)^-$].

Example I

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	100
Powdered. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example II

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	200
Powdered. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example III

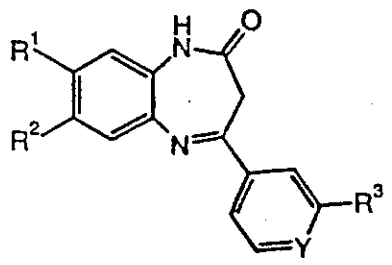
Capsules of the following composition are produced:

	mg/Capsule
Active ingredient	50
Crystalline. lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

Claims

1. Compounds of general formula



I

wherein

R^1 is cyano,
fluoro-lower alkyl,
lower alkoxy,
fluoro-lower alkoxy,
or is pyrrol-1-yl, which is unsubstituted or substitued by one to three substituents selected from the group consisting of
fluoro, chloro, cyano, phenyl, optionally substituted by halogen,
$-(CH_2)_{1-4}$-hydroxy, fluoro-lower alkyl, lower alkyl, $-(CH_2)_n$-lower alkoxy,
$-(CH_2)_n$-C(O)O-R", $-(CH_2)_{1-4}$-NR'R", hydroxy-lower alkoxy and
$-(CH_2)_n$-CONR'R";

R^2 is hydrogen, if R^1 is optionally substituted pyrrol-1-yl as defined above, or is
halogen,
hydroxy,
lower alkyl,
fluoro-lower alkyl,
lower alkoxy,
hydroxymethyl,
hydroxyethoxy,
lower alkoxy-$(ethoxy)_n$ (n = 1 to 4),
lower alkoxymethyl,
cyanomethoxy,
morpholine-4-yl,
thiomorpholine-4-yl,
1-oxothiomorpholine-4-yl,
1,1-dioxothiomorpholine-4-yl,
4-oxo-piperidine-1-yl

4-alkoxy-piperidine-1-yl,
4-hydroxy-piperidine-1-yl,
4-hydroxyethoxy-piperidine-1-yl,
4-lower alkyl-piperazine-1-yl,
alkoxycarbonyl,
2-dialkylamino-ethylsulfanyl,
N,N-bis lower alkylamino lower alkyl,
carbamoylmethyl,
alkylsulfonyl
lower alkoxycarbonyl-lower alkyl,
alkylcarboxy-lower alkyl,
carboxy-lower alkyl,
alkoxycarbonylmethylsulfanyl,
carboxymethylsulfanyl,
1,4-dioxa-8-aza-spiro[4.5]dec-8-yl,
carboxy-lower alkoxy,
cyano-lower alkyl,
2,3-dihydroxy-lower alkoxy,
carbamoylmethoxy,
2-oxo-[1,3]-dioxolan-4-yl-lower alkoxy,
N-(2-hydroxy-lower alkyl)-N-lower alkyl amino,
hydroxycarbamoyl-lower alkoxy,
2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5c]-pyrrol-5-yl,
lower alkoxy-carbamoyl-lower alkoxy,
3R-hydroxy-pyrrolidin-1-yl,
3,4-dihydroxy-pyrrolidin-1-yl,
2-oxo-oxazolidin-3-yl,
lower alkyl-carbamoylmethoxy or
aminocarbamoyl-lower alkoxy;

Y is –CH= or =N-;

R^3 is halogen,
lower alkyl,
fluoro-lower alkyl,
lower alkoxy,
cyano,
$-(CH_2)_n-C(O)-OR''$,

$-(CH_2)_n-C(O)-NR'R''$,

or is an optionally substituted five-membered aromatic heterocycle, which may be substituted by halogen, fluoro-lower alkyl, fluoro-lower alkoxy, cyano, $-(CH_2)_n-NR'R''$, $-(CH_2)_n-C(O)-OR''$, $-(CH_2)_n-C(O)-NR'R''$, $-(CH_2)_n-SO_2-NR'R''$, $-(CH_2)_n-C(NH_2)=NR''$, hydroxy, lower alkoxy, lower alkylthio, or by lower alkyl, which is optionally substituted by fluoro, hydroxy, lower alkoxy, cyano or carbamoyloxy;

R' is hydrogen,
lower alkyl,
C_3-C_6-cycloalkyl,
fluoro-lower alkyl or
2-lower alkoxy lower alkyl;

R'' is hydrogen,
lower alkyl,
C_3-C_6-cycloalkyl,
fluoro-lower alkyl,
2-lower alkoxy lower alkyl,
$-(CH_2)_{2-4}$-di-lower alkylamino,
$-(CH_2)_{2-4}$-morpholinyl,
$-(CH_2)_{2-4}$-pyrrolidinyl,
$-(CH_2)_{2-4}$-piperidinyl or
3-hydroxy-lower alkyl;

n is 0, 1, 2, 3 or 4;

and their pharmaceutically acceptable addition salts.

2. Compounds according to claim 1, wherein R^1 is trifluoromethyl.

3. Compounds according to claim 2, wherein R^2 is morpholine.

4. Compounds according to claims 2 and 3, wherein the compounds are selected from the group consisting of

4-(8-morpholin-4-yl-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile,

4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-[3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-[3-(3-hydroxymethyl-isoxazol-5-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one, and

4-[3-(5-hydroxymethyl-isoxazol-3-yl)-phenyl]-7-morpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

5. Compounds according to claim 2, wherein R^2 is thiomorpholine.

6. Compounds according to claims 2 and 5, wherein the compounds are selected from the group consisting of

4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-7-thiomorpholin-4-yl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one, and

4-(4-oxo-8-thiomorpholin-4-yl-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile.

7. Compounds according to claim 2, wherein R^2 is lower alkoxy.

8. Compounds according to claims 2 and 7, wherein the compounds are selected from the group consisting of

7-methoxy-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-methoxy-4-[3-(5-pyrrolidin-1-ylmethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-(8-ethoxy-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile,

4-[3-(5-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-7-ethoxy-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-ethoxy-4-(3-{5-[(2,2,2-trifluoro-ethylamino)-methyl]-[1,2,3]triazol-1-yl}-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-ethoxy-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one, and

7-methoxy-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

9. Compounds according to claim 2,- wherein R^2 is lower alkyl or halogen.

10. Compounds according to claims 2 and 9, wherein the compounds are selected from the group consisting of

4-(8-methyl-4-oxo-7-trifluoromethyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-pyridine-2-carbonitrile,

7-chloro-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-chloro-4-[3-(5-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-[3-(5-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-methyl-4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-chloro-4-(3-[1,2,4]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-chloro-4-(3-imidazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-chloro-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-methyl-4-(3-[1,2,4]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-(3-imidazol-1-yl-phenyl)-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

7-methyl-4-(3-[1,2,3]triazol-1-yl-phenyl)-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-[3-(2-hydroxymethyl-5-methyl-thiazol-4-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one, and

4-[3-(4-hydroxymethyl-thiazol-2-yl)-phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

11. Compounds according to claim 1, wherein R^1 is unsubstituted pyrrol-1-yl.

12. Compounds according to claim 11, wherein R^2 is hydrogen, halogen, lower alkoxy-ethoxy or lower alkoxy.

13. Compounds according to claims 11 and 12, wherein the compounds are selected from the group consisting of

4-(3-iodo-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-(3-imidazol-1-yl-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-[3-(4-hydroxymethyl-thiazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

8-pyrrol-1-yl-4-(3-[1,2,3]triazol-1-yl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

4-(3-oxazol-2-yl-phenyl)-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one,

5-[3-(4-oxo-7-pyrrol-1-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-phenyl]-oxazole-4-carboxylic acid ethyl ester,

4-[3-(4-hydroxymethyl-oxazol-2-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one, and

4-[3-(3-methyl-isoxazol-5-yl)-phenyl]-8-pyrrol-1-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

14. Compounds according to claim 1, wherein R^1 is substituted pyrrol-1-yl.

15. Compounds according to claim 14, wherein R^2 is hydrogen or lower alkoxy.

16. Compounds according to claims 14 and 15, wherein the compounds are selected from the group consisting of

4-(2-chloro-phenyl)-1-[2-(3-cyano-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-7-yl]-1H-pyrrole-3-carbonitrile,

3-[4-oxo-7-(3-phenyl-pyrrol-1-yl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile, and

3-[7-(2-tert.-butyl-pyrrol-1-yl)-8-methoxy-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile.

17. Compounds according to claim 1, wherein R^1 is cyano.

18. Compounds according to claim 1, wherein R^2 is morpholine or thiomorpholine.

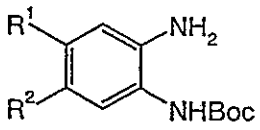
19. Compounds according to claim 1, wherein R^3 is cyano or an optionally substituted five-membered aromatic heterocycle.

20. A medicament containing one or more compounds of any one of claims 1 to 19 and pharmaceutically acceptable excipients.

21. A medicament according to claim 20 for the treatment or prevention of acute and/or chronic neurological disorders including psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits.

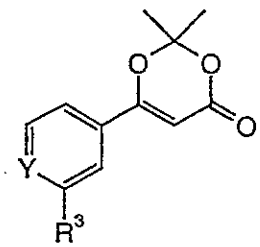
22. A process for preparing compounds of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula II



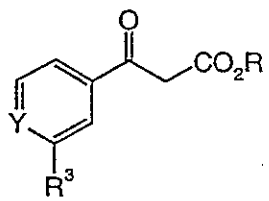
II

with a compound of formula IV or IVa



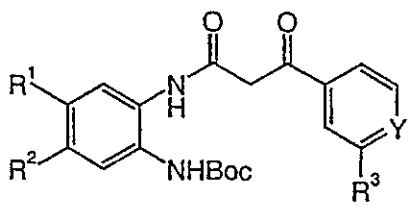
IV

or



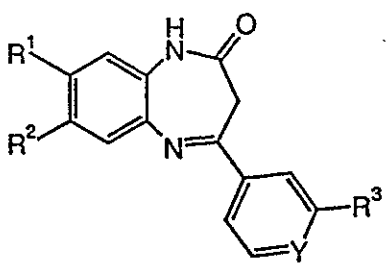
IVa

wherein R is lower alkyl, prefereably ethyl or tert.-butyl, to a compound of formula III



III

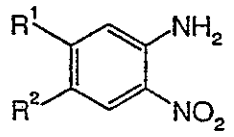
which subsequently undergoes deprotection of the amino group and cyclization, to obtain a compound of formula I



I

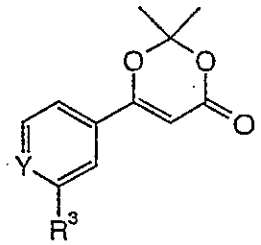
wherein R^1, R^2, R^3 and Y are as described above, or

b) reacting a compound of formula VI



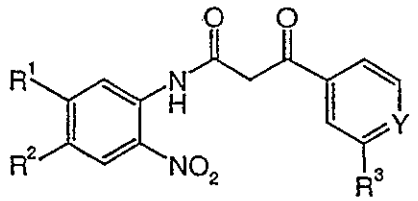
VI

with a compound of formula IV



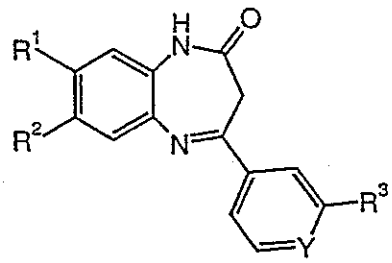
IV

to a compound of formula V



V

which subsequently undergoes reduction of the nitro group and cyclization, to obtain a compound of formula I



I

wherein R^1, R^2, R^3 and Y are as described above and, if desired,
converting the compound obtained into a pharmaceutically acceptable acid addition salt.

23. A compound according to any one of claims 1 to 19, whenever prepared by a process as claimed in claim 22 or by an equivalent method.

24. A compound according to any one of claims 1 to 19 for the treatment or prevention of diseases.

25. The use of one or more compounds according to claims 1 to 19 and/or one or more of their pharmaceutically acceptable acid addition salts for the manufacture of medicaments for the treatment or prevention of acute and/or chronic neurological disorders including psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits.

26. The invention as hereinbefore described.

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