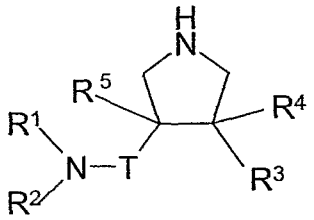
3,4-SUBSTITUTED PYRROLIDINE DERIVATIVES FOR THE TREATMENT OF HYPERTENSION

The invention relates to the use of (3,4-di-, 3,3,4,- tri, 3,4,4-tri- or 3,3,4,4-tetra-)substituted pyrrolidine compounds for the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin; the use of a compound of that class in the treatment of a disease that depends on activity of renin; compounds that are part of a subclass of these substituted pyrrolidine compounds for use in the diagnostic and therapeutic treatment of a warm-blooded animal, especially for the treatment of a disease (= disorder) that depends on activity of renin; new compounds that are part of a subclass of these substituted pyrrolidine compounds; pharmaceutical formulations or products comprising said substituted pyrrolidine compounds, and/or a method of treatment comprising administering said substituted pyrrolidine compounds, a method for the manufacture especially of said new substituted pyrrolidine compounds, as well as novel intermediates, starting materials and/or partial steps for their synthesis.

Especially, the invention relates to the use of a compound of the formula I,



(I)

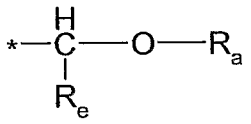
as described in the claims or wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

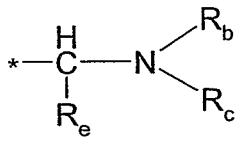
R^3 is a moiety selected from the group of moieties of the formulae

(a)

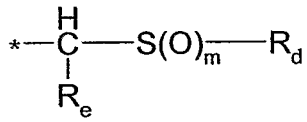


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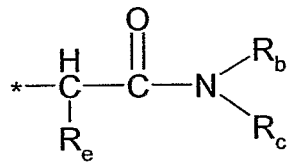
(b)



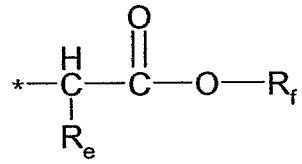
(c)



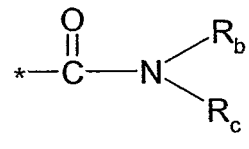
(d)



(e)

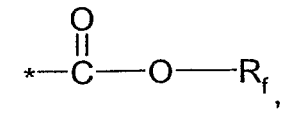


(f)



and

(g)



,

where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;
R_b and R_c are independently selected from the moieties given under R_a, with the proviso that preferably not more than one of R_b and R_c is acyl,
Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (preferably if m is 0) acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;
R_e is hydrogen, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (especially) substituted or preferably unsubstituted C_1-C_7-alkyl; and
R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;
m is 0, 1 or 2;
each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;
and T is methylene ($-CH_2-$), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-) , carbonyl (-C(=O)-) or thiocarbonyl (-C(=S)-);
or a pharmaceutically acceptable salt thereof,
in the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin, especially hypertension.

The compounds of the present invention exhibit inhibitory activity on the natural enzyme renin. Thus, compounds of formula I may be employed for the treatment (this term also including prophylaxis) of one or more disorders or diseases selected from, *inter alia*, hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome,

diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders, especially as far as these diseases can be modulated (more especially beneficially influenced) by renin inhibition.

Listed in the claims and below are definitions of various terms used to describe the compounds of the present invention as well as their use and synthesis, starting materials and intermediates and the like. These definitions, either by replacing one, more than one or all general expressions or symbols used in the present disclosure and thus yielding preferred embodiments of the invention, preferably apply to the terms as they are used throughout the specification unless they are otherwise limited in specific instances either individually or as part of a larger group.

The term "lower" or "C_1-C_7-" defines a moiety with up to and including maximally 7, especially up to and including maximally 4, carbon atoms, said moiety being branched (one or more times) or straight-chained and bound via a terminal or a non-terminal carbon. Lower or C_1-C_7-alkyl, for example, is n-pentyl, n-hexyl or n-heptyl or preferably C_1-C_4-alkyl, especially as methyl, ethyl, n-propyl, sec-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl.

Halo or halogen is preferably fluoro, chloro, bromo or iodo, most preferably fluoro, chloro or bromo. If not explicitly or implicitly stated otherwise, halo can also stand for more than one halogen substituent in moieties such as alkyl, alkanoyl and the like (e.g. in trifluoromethyl, trifluoroacetyl).

Unsubstituted or substituted mono- or bicyclic aryl preferably is a mono- or bicyclic aryl with 6 to 22 carbon atoms, especially phenyl, indenyl or naphthyl, and is unsubstituted or substituted by one or more, especially one to three, moieties, preferably independently selected from the group consisting of

a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H (especially in substituted aryl or substituted aryl-alkyl as R^1) where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or (with lower preference) substituted e.g. by one or more

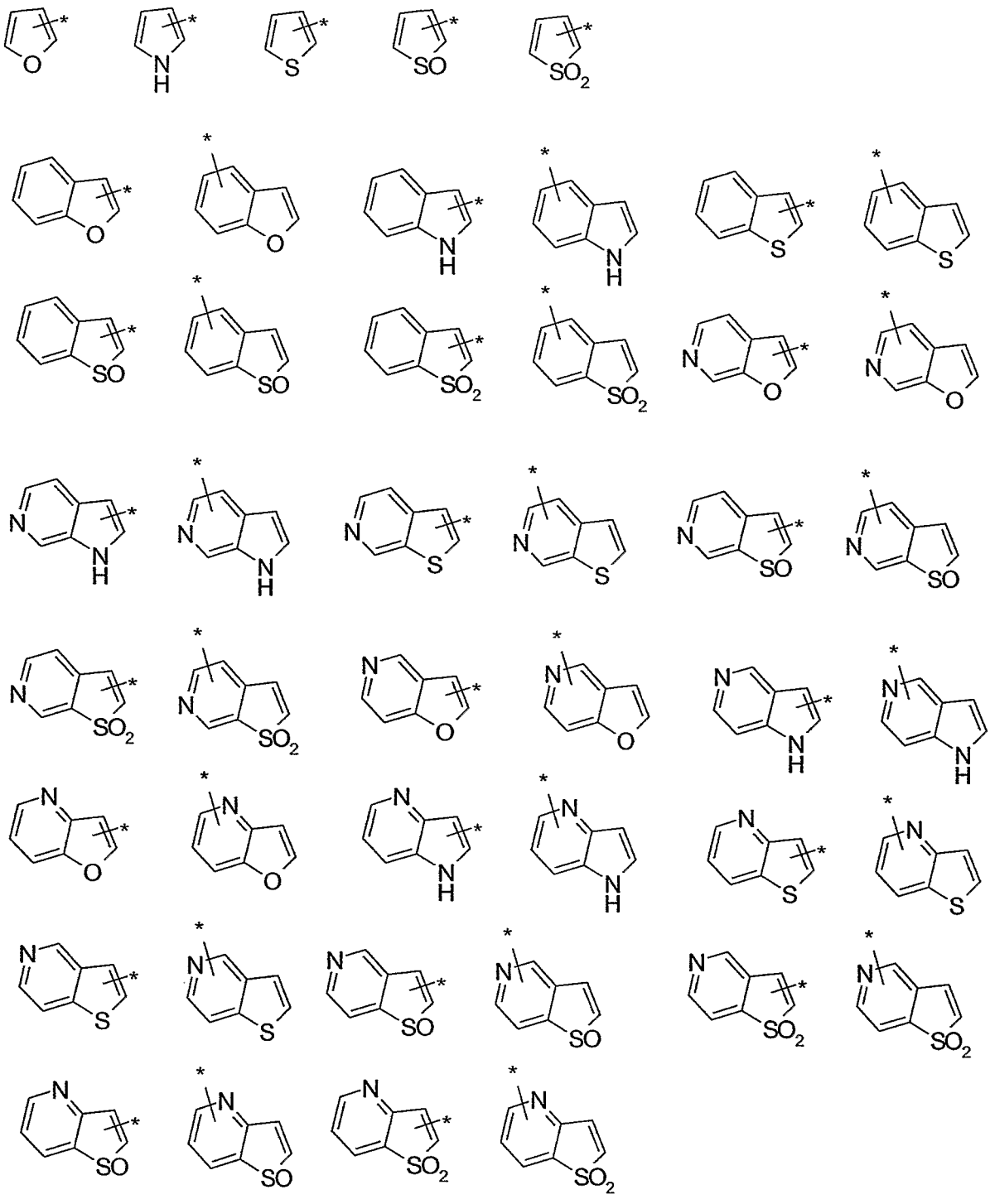
moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkanoyl, naphthyl-C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; e.g. C_1-C_7-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, such as 3-methoxypropyl or 2-methoxyethyl, C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyloxy- or naphthyloxy-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, such as aminomethyl, C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl, mono- or di- (C_1-C_7-alkyl-, naphthyl-, phenyl, naphthyl-C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-O-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-SO_2-NH-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7alkoxy, C_1-C_7-alkanoyloxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyloxy, halo-C_1-C_7-alkylthio, such as trifluoromethylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, mono- or di-(C_1-C_7-alkyl-, naphthyl-C_1-C_7-alkyl-, phenyl-C_1-C_7-alkyl- and/or C_1-C_7-alkoxy-C_1-C_7-alkyl-)amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkanoylamino, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonylamino, carboxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkoxycarbonyl, amino-C_1-C_7-alkoxycarbonyl, (N-) mono-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkoxycarbonyl, N-mono- or N,N-di-(C_1-C_7-alkyl, naphthyl-C_1-C_7.alkyl and/ or phenyl-C_1-C_7-alkyl)-aminocarbonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, amino-C_1-C_7-alkylsulfonyl, N-mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylsulfonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylsulfonyl, N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl or N-mono- or N,N-di-(C_1-C_7-alkyl)-aminosulfonyl;

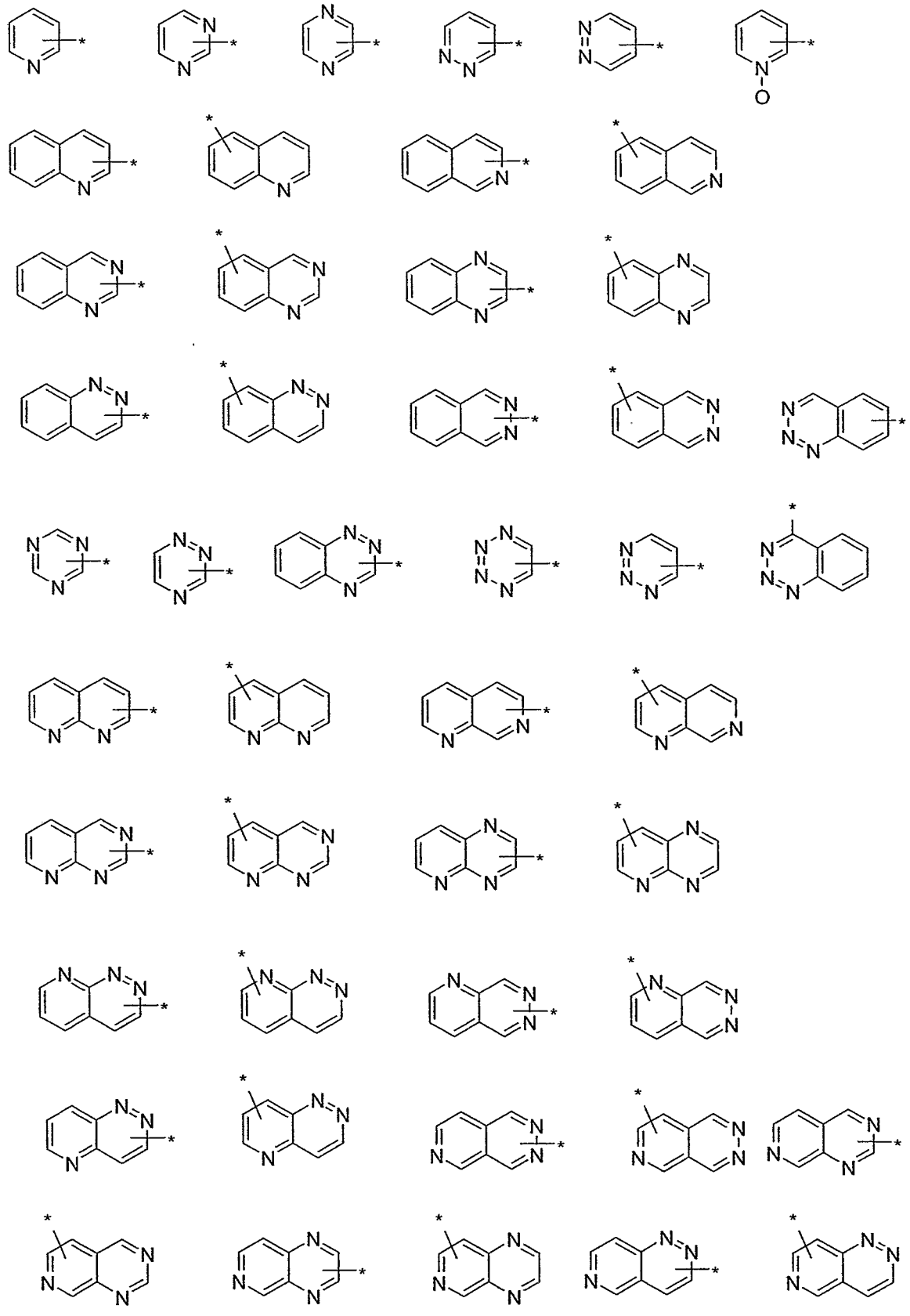
from C_2-C_7-alkenyl, C_2-C_7-alkynyl, phenyl, naphtyl, mono- or bicyclic heterocyclyl, especially as defined below for mono- or bicyclic heterocyclyl, preferably selected from pyrrolyl, furanyl,

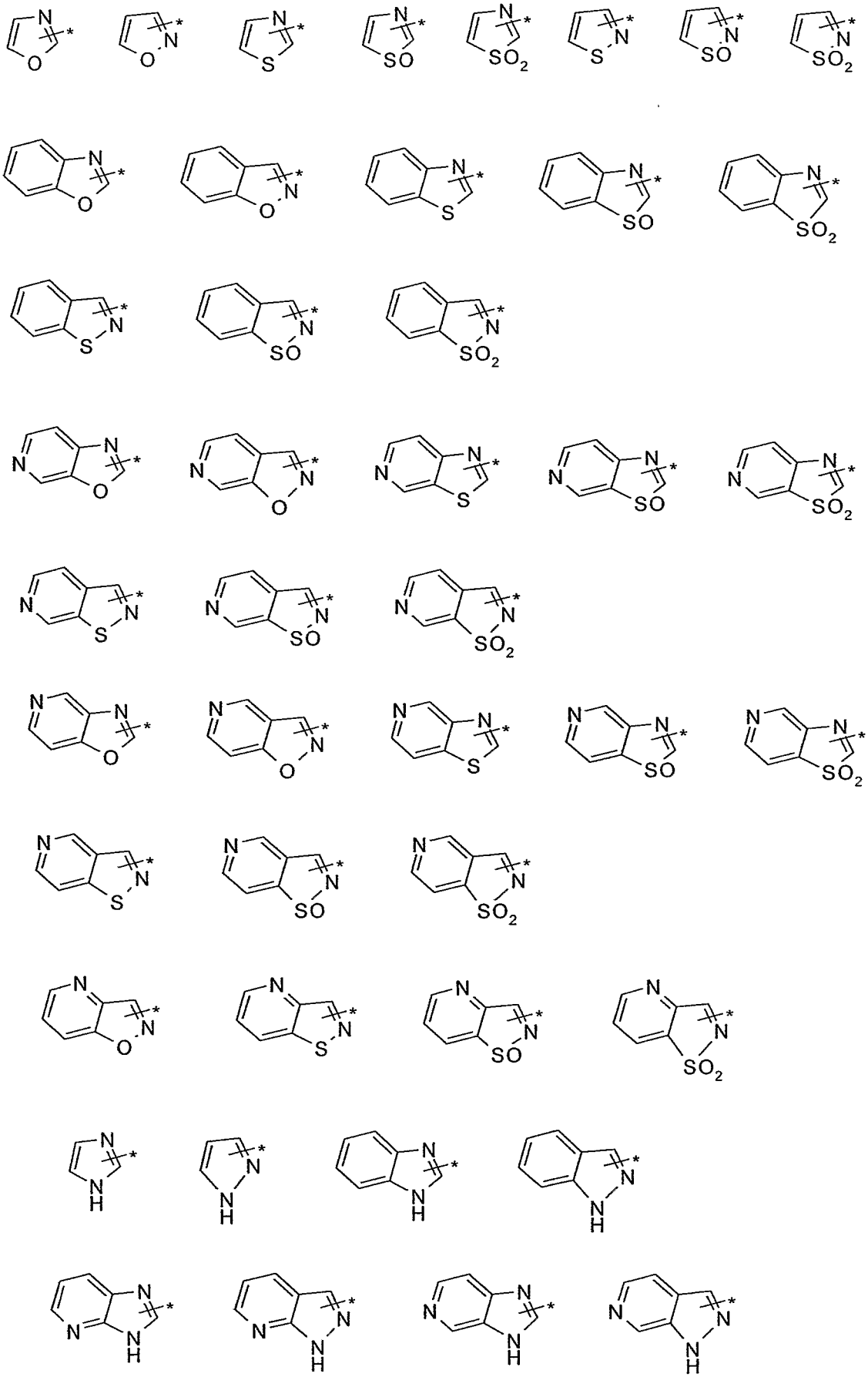
thienyl, pyrimidine-2,4-dione-1-, -3- or –5-yl and tetrahydrofuranyl, , phenyl- or naphthyl- or (mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl or C_1-C_7-alkyloxy wherein mono- or bicyclic heterocyclyl is as defined below, preferably selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl ; such as benzyl or naphthylmethyl, tetrahydrofuranyl- or tetrahydropyranyl-C_1-C_7-alkyloxycarbonyl, benzoyl- or naphthoylamino-C_1-C_7-alkyl, (phenyl- or naphthyl- or mono- or bicyclic heterocyclyl)-sulfonylamino-C_1-C_7-alkyl wherein phenyl or naphthyl or mono- or bicyclic heterocyclyl is unsubstituted or substituted, preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, halo, hydroxy, phenyl-C_1-C_7-alkoxy wherein phenyl is preferably unsubstituted or substituted, preferably by C_1-C_7-alkoxy and/or halo, mono- or bicyclic heterocyclyl-C_1-C_7-alkoxy, (mono- or bicyclic heterocyclyl or phenyl or naphthyl)-oxy, naphthyl-C_1-C_7-alkyloxy, benzoyl or naphthoyl or mono- or bicyclic heterocyclylcarbonyl)-oxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonyloxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-thio, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-thio, nitro, amino, di-((naphthyl or phenyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl)-amino, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-amino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxycarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyloxycarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, amino-C_1-C_7-alkylcarbonyl, (N-) mono- or (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylcarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxy-carbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkoxycarbonyl, (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono or N,N-di-(naphthyl or phenyl or mono- or bicyclic heterocyclyl)-aminocarbonyl, cyano, C_1-C_7-alkylene which is unsubstituted or substituted by up to four C_1-C_7-alkyl substituents and bound to two adjacent ring atoms of the aryl moiety, sulfenyl, sulfinyl, C_1-C_7-alkylsulfinyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfinyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, (phenyl or naphthyl or mono- or bicyclic

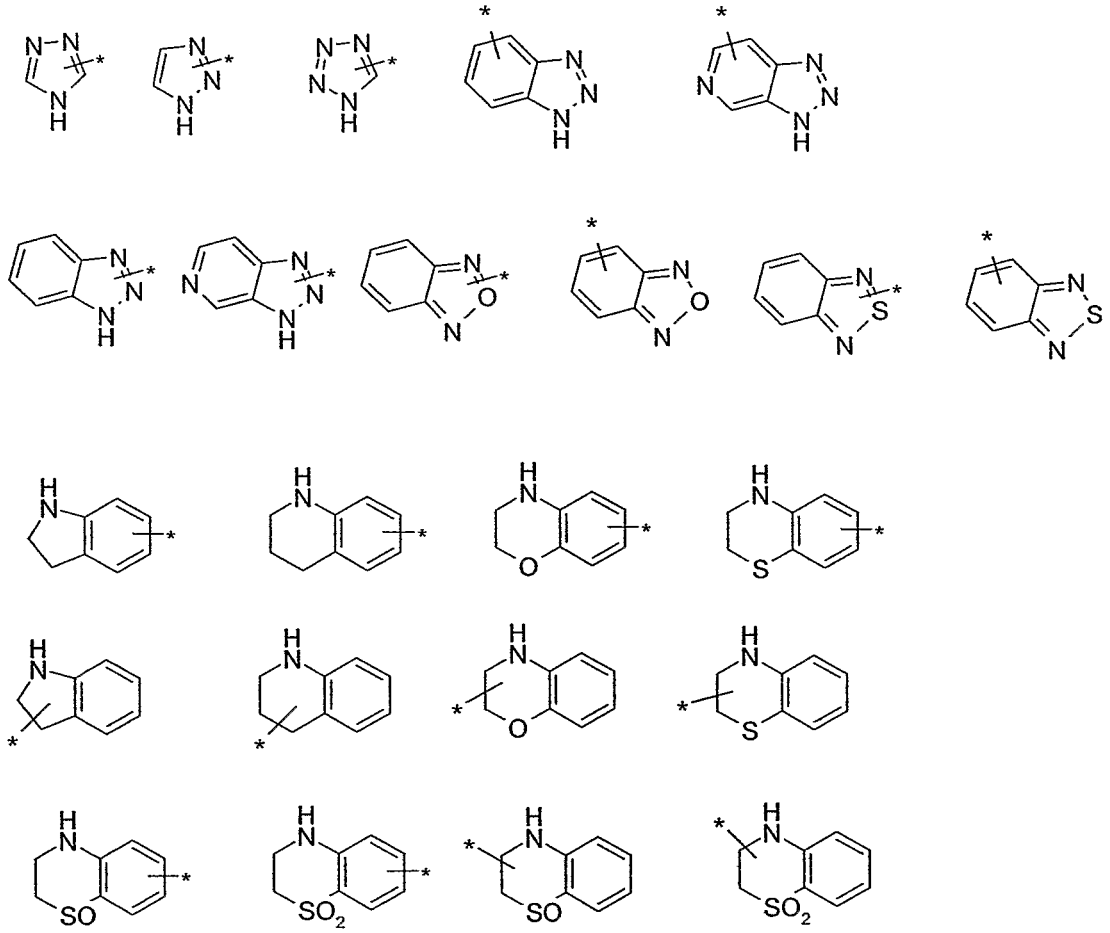
heterocyclyl)-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, mono- or bicyclic heterocyclyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl-C_1-C_7-alkyl)-aminosulfonyl;

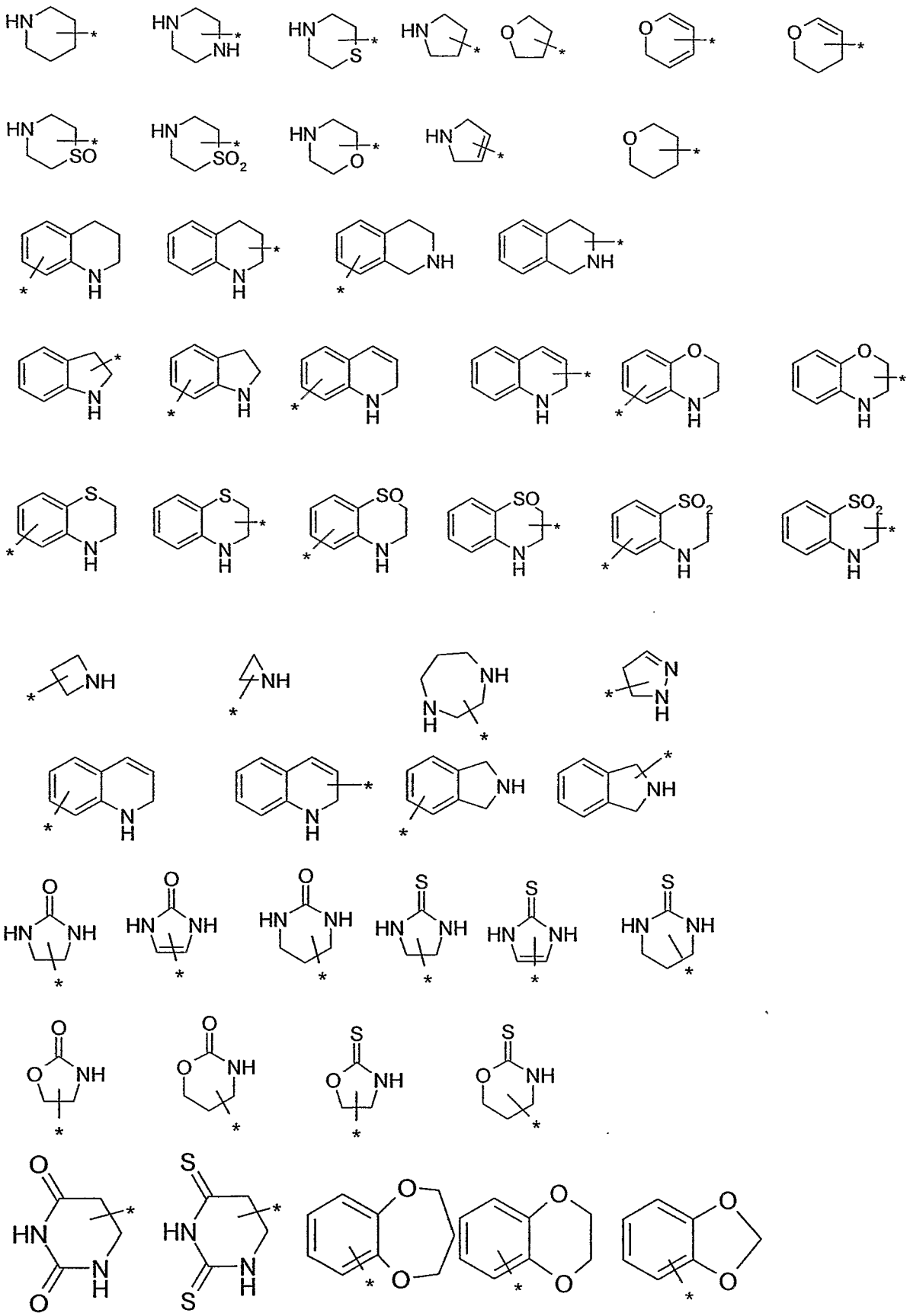
where any phenyl or naphthyl or mono- or bicyclic heterocyclyl (which mono- or bicyclic heterocyclyl is preferably as defined for mono- or bicyclic heterocyclyl, more preferably is selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl) mentioned as substituent of or as part of a substituent of substituted aryl is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, halo, especially fluoro, chloro, bromo or iodo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents.Unsubstituted or substituted mono- or bicyclic heterocyclyl is a mono- or bicyclic heterocyclic moiety with an unsaturated, partially saturated or saturated ring system with preferably 3 to 22 (more preferably 3 to 14) ring atoms and with one or more, preferably one to four, heteroatoms independently selected from nitrogen (=N-, -NH- or substituted –NH-), oxygen and sulfur (-S-, S(=O)- or S-$(=O)_2$-) which is unsubstituted or substituted by one or more, e.g. up to three, substitutents preferably independently selected from the substitutents mentioned above for aryl and from oxo (=O) and thioxo (=S). Preferably, unsubstituted or substituted mono- or bicyclic heterocyclyl is selected from the following moieties:

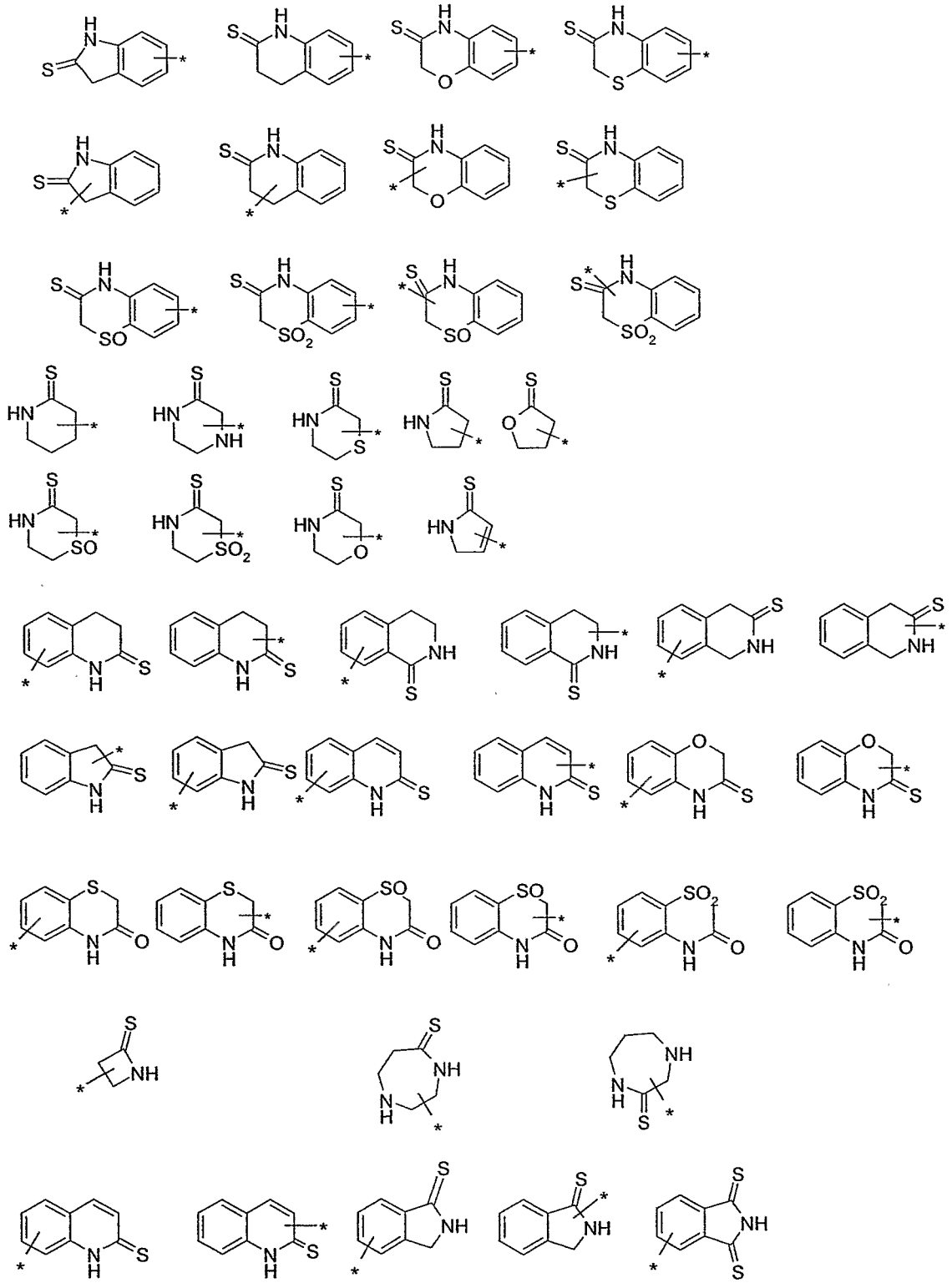


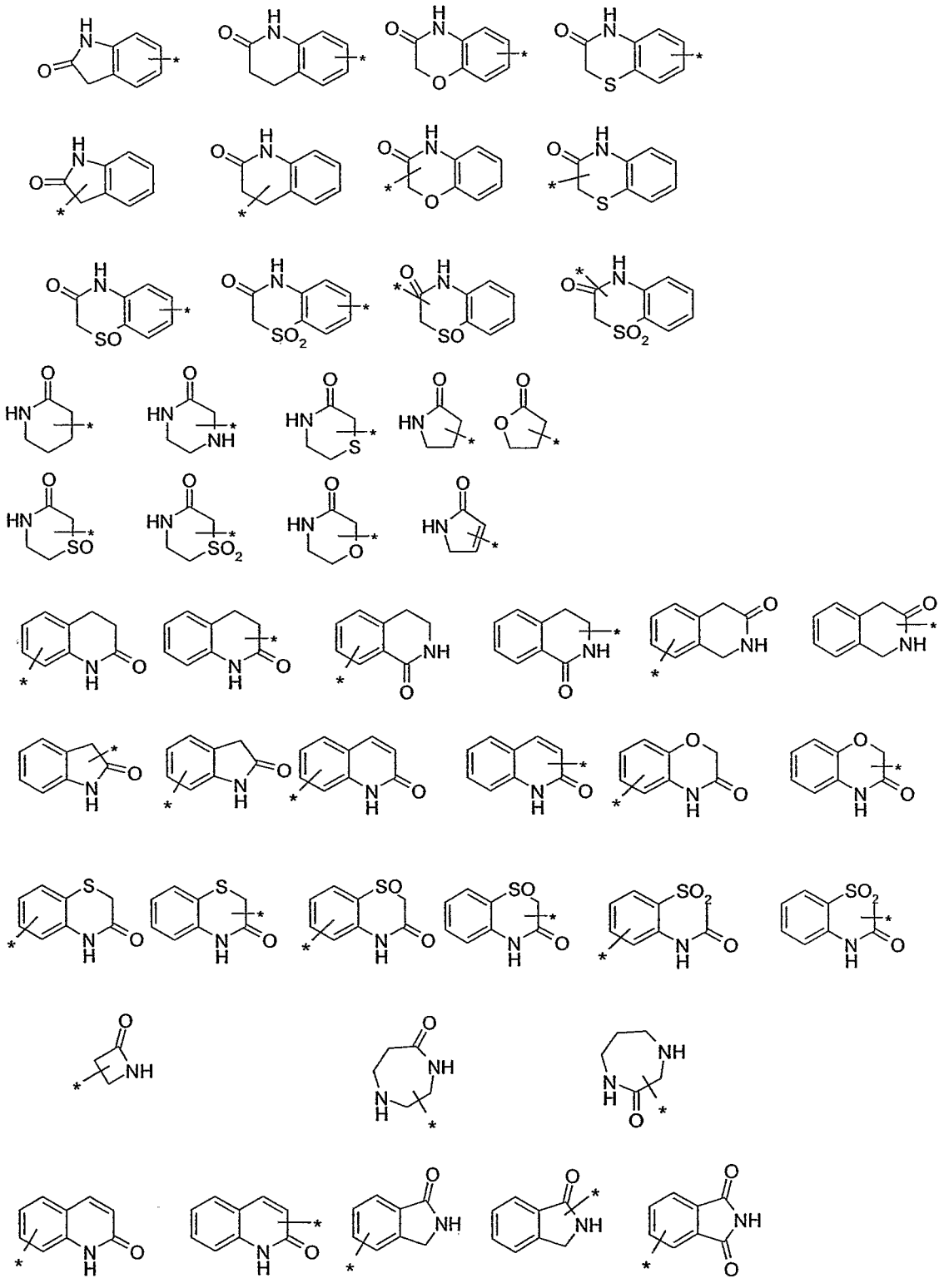












where in each case where an NH is present the bond with the asterisk connecting the respective heterocyclyl moiety to the rest of the molecule the H may be replaced with said

bond and/or the H may be replaced by a substituent (thus forming substituted imino), and one or more substituents may be present as just described.

Unsubstituted or substituted mono- or bicyclic cycloalkyl is preferably mono- or bicyclic, more preferably monocyclic, C_3-C_{16}, more preferably C_3-C_{10}-cycloalkyl, which may include one or more double (e.g. in cycloalkenyl) and/or triple bonds (e.g. in cycloalkinyl) with less double and/or triple bonds than required to form a fully unsaturated ring (e.g. aryl) system. Preferably, mono- or bicyclic cycloalkyl is saturated. The mono- or bicyclic cycloalkyl is unsubstituted or substituted by one or more, e.g. one to three substitutents preferably independently selected from those mentioned above as substituents for aryl.

In unsubstituted or substituted mono- or bicyclic aryl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic aryl (which is preferably unsubstituted or substituted by one or more substituents, e.g. one to three substituents independently selected from those mentioned above as substituents for aryl) is preferably as described above for aryl and is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above.

In unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic heterocyclyl is preferably as described above and is unsubstituted or substituted by one or more, e.g. up to three, substitutents independently selected from those mentioned above for substituted aryl, and heterocyclyl is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above.

In unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic cycloalkyl is preferably as described above and is unsubstituted or substituted by one or more, e.g. up to three, substitutents independently selected from those mentioned above for substituted aryl, and cycloalkyl is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-

alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above.

Acyl is preferably unsubstituted or substituted mono- or bicyclic aryl-carbonyl or -sulfonyl, unsubstituted or substituted mono- or bicyclic heterocyclylcarbonyl or -sulfonyl, unsubstituted or substituted mono- or bicyclic cycloalkylcarbonyl or -sulfonyl, formyl or (unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl or unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl)-carbonyl or -sulfonyl, or (especially if bound to N, S or O) unsubstituted or substituted alkyloxycarbonyl ,unsubstituted or substituted mono- or bicyclic aryl-oxycarbonyl, unsubstituted or substituted mono- or bicyclic heterocyclyloxycarbonyl, unsubstituted or substituted mono- or bicyclic cyclo-alkyloxycarbonyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-oxycarbonyl , unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-oxycarbonyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-oxycarbonyl or N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl or -aminosulfonyl, with the proviso that–oxycarbonyl bound moieties are preferably bound to a nitrogen in the rest of the molecule. Examples of preferred acyl moieties other than R^1 and/or R^2 (e.g. R_a, R_b, R_c and/or R_d) are C_1-C_7-alkanoyl, (such as acetyl, 3,3-dimethyl-butyryl, 2,2-dimethyl-propionyl or 3,3-dimethyl-butyryl, unsubstituted (or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted)-phenyl-C_1-C_7-alkanoyl (e.g. the corresponding unsubstituted or substituted benzoyl or phenylacetyl) such as benzoyl or phenylacetyl, C_3-C_8-cycloalkyl-carbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyll, such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclohexylacetyl or cyclohexylcarbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, such as tetrahydrofuranyl-carbonyl, tetrahydropyranylcarbonyl, tetrahydrofuranylacetyl or tetrahydropyranylacetyl, unsubstituted or mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted) (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, such as phenylsulfonyl (= benzenesulfonyl) or phenylmethanesulfonyl, C_1-C_7-alkylsulfonyl, such as

methylsulfonyl (= methanesulfonyl), ((N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl (e.g. benzyl)]-aminocarbonyl, N-[C_3-C_8-cycloalkyl (e.g. cyclohexyl-), C_3-C_8-cycloalkyl-C_1-C_7-alkyl]aminocarbonyl, C_1-C_7-alkylaminocarbonyl or (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, napthyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl selected preferably from pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazanyl, benzofuranyl, benzothiophenyl, (more preferably) isoquinolinyl, quinolinyl and indolyl)-oxycarbonyl, e.g. C_1-C_7-alkoxycarbonyl, such as tert-butyloxycarbonyl, isobutyloxycarbonyl or phenyl-C_1-C_7-alkyloxycarbonyl. As acyl R^1 or R^2, indolyl-C_1-C_7-alkanoyl, e.g. indolylcarbonyl, quinolyl-C_1-C_7-alkanoyl, e.g. quinolinylcarbonyl, or phenyl-C_1-C_7-alkanoyl, e.g. phenylacetyl, wherein indolyl, quinolyl and phenyl are unsubstituted or substituted by a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or (with lower preference) substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; and optionally one or more, e.g. up to two, further substituents selected from the other substituents mentioned for substituted aryl. Unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl and unsubstituted or substituted mono- or bicyclic cycloalkyl are preferably as defined above whereever they are mentioned as part of acyl, unsubstituted or substituted alkyl is preferably as defined below.

Unsubstituted or substituted alkyl is preferably C_1-C_{20}-alkyl, more preferably C_1-C_7-alkyl, that is straight-chained or branched (one or, where appropriate, more times), which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from

unsubstituted or substituted mono- or bicyclic heterocyclyl as described below, especially pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazanyl, benzofuranyl, benzothiophenyl, , (more preferably) isoquinolinyl, quinolinyl or especially indolyl, each of which is unsubstituted or substituted as described above for unsubstituted or substituted heterocyclyl, e.g. by one to three substitutents independently selected from halo, hydroxy, such as chloro, C_1-C_7-alkyl, such as methyl, cyano and C_1-C_7-alkanoyl, such as acetyl; from unsubstituted or substituted mono- or bicyclic cycloalkyl as described above, especially cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl each of which is unsubstituted or substituted as described below for unsubstituted or substituted cycloalkyl; or especially from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, C_1-C_7-alkanoyloxy, (C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonyloxy, benzoyl- or naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, such as trifluoromethylthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino ****, benzoyl- or naphthoylamino**--**, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino), phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkylcarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl (-S-OH), sulfonyl (-S(=O)-OH), C_1-C_7-alkylsulfinyl (C_1-C_7-alkyl-S(=O)-), phenyl- or naphthylsulfinyl, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonylamino or –aminocarbonyloxy and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino;

where any phenyl or naphthyl mentioned as substituent of or as part of a substituent of substituted alkyl is unsubstituted or substituted by one or more, preferably up to three,

moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, halo, especially fluoro, chloro, bromo or iodo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents.

Unsubstituted or substituted alkenyl is preferably C_2-C_{20}-alkenyl, more preferably C_2-C_7-alkenyl with one or, if possible, more double bonds, that is straight-chained or branched (one or, where appropriate, more times), which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from those mentioned as substituents for substituted alkyl and from unsubstituted or substituted mono- or bicyclic aryl, each preferably as described above. Substituents with an active hydrogen (e.g. hydroxy or amino) are preferably present in the form of tautomers in equilibrium if bound directly to a carbon with a double bond, preferably at such positions substituents with active hydrogen are avoided.

Unsubstituted or substituted alkynyl is preferably C_2-C_{20}-alkynyl, more preferably C_2-C_7-alkynyl with one or, if possible, more triple bonds, that is straight-chained or branched (one or, where appropriate, more times), which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from those mentioned as substituents for subsituted alkyl and from unsubsituted or substituted mono- or bicyclic aryl, each preferably as described above. Substituents with an active hydrogen (e.g. hydroxy or amino) are preferably present in the form of tautomers in equilibrium if bound directly to a carbon with a triple bond, preferably at such positions substituents with active hydrogen are avoided.

Esterified hydroxy is preferably acyloxy with acyl as defined above, more preferably C_1-C_7-alkanoyloxy or benzoyloxy.

Etherified hydroxy is preferably substituted C_1-C_7-alkyloxy wherein substituted alkyl is preferably as defined above, unsubstituted or substituted mono- or bicyclic aryloxy, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyloxy, unsubstituted or substituted mono- or bicyclic heterocyclyloxy, unsubstituted or substituted mono- or bicyclic heterocyclyloxy-C_1-C_7-alkyloxy, unsubstituted or substituted mono- or bicyclic cycloalkyloxy or unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyloxy (where in each case the moieties are preferably defined as above) or more preferably unsubstituted alkyloxy, especially C_1-C_7-alkyloxy.

Where an asterisk (*) marks a the bond binding a moiety, the corresponding bond is that shown in the corresponding formula of the respective compound of the formula I (or a precursor thereof) binding the respective moiety.

The preceding and especially the following preferred embodiments of the moieties and symbols in formula I can be employed independently of each other to replace more general definitions and thus to define specially preferred embodiments of the invention, where the remaining definitions can be kept broad as defined in embodiments of the inventions defined above of below.

Preferably, not more than one of R_1 and R_2 is acyl, the other has one of the meanings given hereinabove or hereinbelow for these moieties other than acyl.

As R^3, moieties of the formulae (a), (b), (c), (f) and slightly less (g), more preferably of the formulae (a), (b) or (f), are especially preferred.

The symbol m preferably stands for 0 or 2.

R_d preferably is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, or (if m = 2) is $-N(R_b)(R_c)$ wherein R_b and R_c are as defined above or below.

R_e is preferably hydrogen.

Preferably, at least one of R^4 and R^5 is hydrogen (i.e. the preferred compounds of the invention are (3,4-di-, 3,3,- tri, 3,4,4-tri-)substituted pyrrolidines), more preferably both are hydrogen.

In all definitions above and below the person having skill in the art will, without undue experimentation or considerations, be able to recognize which are relevant (e.g. those that if present provide compounds that are sufficiently stable for the manufacture of pharmaceuticals, e.g. having a half-life of more than 30 seconds) and thus are preferably encompassed by the present claims and that only chemically feasible bonds and substitutions (e.g. in the case of double or triple bonds, hydrogen carrying amino or hydroxy groups and the like) are encompassed, as well as tautomeric forms where present, especially in equilibrium. For example, preferably, for reasons of stability or chemical feasibility, directly vicinal atoms in chains preferably are not selected from oxy plus oxy, thio plus oxy, oxy plus thio or thio plus thio, except where ring systems or the like are present that are sufficiently stable. Substitutents binding via an O (e.g. in C_1-C_7-alkoxy) or S that is part of them are preferably not bound to nitrogen e.g. in rings.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I. They can be formed where salt forming groups, such as basic or acidic groups, are present that can exist in dissociated form at least partially, e.g. in a pH range from 4 to 10 in aqueous solutions, or can be isolated especially in solid, especially crystalline, form.

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom (e.g. imino or amino), especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, lactic acid, fumaric acid, succinic acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, benzoic acid, methane- or ethane-sulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, N-cyclohexylsulfamic acid, N-

methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

In the presence of negatively charged radicals, such as carboxy or sulfo, salts may also be formed with bases, e.g. metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example triethylamine or tri(2-hydroxyethyl)amine, or heterocyclic bases, for example N-ethyl-piperidine or N,N'-dimethylpiperazine.

When a basic group and an acid group are present in the same molecule, a compound of formula I may also form internal salts.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable comprised in pharmaceutical preparations), and these are therefore preferred.

In view of the close relationship between the compounds in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the compounds or salts thereof, any reference to "compounds", "starting materials" and "intermediates" hereinbefore and hereinafter, especially to the compound(s) of the formula I or their precursors, is to be understood as referring also to one or more salts thereof or a mixture of a corresponding free compound and one or more salts thereof, each of which is intended to include also any solvate, metabolic precursor such as ester or amide of the compound of formula I, or salt of any one or more of these, as appropriate and expedient and if not explicitly mentioned otherwise. Different crystal forms may be obtainable and then are also included.

Where the plural form is used for compounds, starting materials, intermediates, salts, pharmaceutical preparations, diseases, disorders and the like, this is intended to mean one (preferred) or more single compound(s), salt(s), pharmaceutical preparation(s), disease(s), disorder(s) or the like, where the singular or the indefinite article ("a", "an") is used, this is

intended to include the plural (for example also different configuration isomers of the same compound, e.g. enantiomers in racemates or the like) or preferably the singular ("one").

The compounds of the present invention can possess two or more asymmetric centers depending on the choice of the substituents. The preferred absolute configurations are as indicated herein specifically. However, any possible isolated or pure diastereoisomers, enantiomers or geometric enantiomers, and mixtures thereof, e.g., mixtures of enantiomers, such as racemates, are encompassed by the present invention.

As described above, the present invention provides in some of its important embodiments the use of (3,4-di-, 3,4,4-tri- or 3,3,4,4-tetra-)substituted pyrrolidine compounds for the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin; the use of a compound of that class in the treatment of a disease that depends on activity of renin; compounds that are part of a subclass of these substituted pyrrolidine compounds for use in the diagnostic and therapeutic treatment of a warm-blooded animal, especially for the treatment of a disease (= disorder) that depends on activity of renin; new compounds that are part of a subclass of these substituted pyrrolidine compounds; pharmaceutical formulations comprising said substituted pyrrolidine compounds, and/or a method of treatment comprising administering said substituted pyrrolidine compounds, a method for the manufacture especially of said new substituted pyrrolidine compounds, as well as novel intermediates, starting materials and/or partial steps for their synthesis.

"Inappropriate" renin activity preferably relates to a state of a warm-blooded animal, especially a human, where renin shows a renin activity that is too high in the given situation (e.g. due to one or more of misregulation, overexpression e.g. due to gene amplification or chromosome rearrangement or infection by microorganisms such as virus that express an aberrant gene, abnormal activity e.g. leading to an erroneous substrate specificity or a hyperactive renin e.g. produced in normal amounts, too low activity of renin activity product removing pathways, high substrate concentration and/or the like) and/or leads to or supports a renin dependent disease or disorder as mentioned above and below, e.g. by too high renin activity. Such inappropriate renin activity may, for example, comprise a higher than normal activity, or further an activity in the normal or even below the normal range which, however, due to preceding, parallel and or subsequent processes, e.g. signaling, regulatory effect on

other processes, higher substrate or product concentration and the like, leads to direct or indirect support or maintenance of a disease or disorder, and/or an activity that supports the outbreak and/ or presence of a disease or disorder in any other way. The inappropriate activity of renin may or may not be dependent on parallel other mechanisms supporting the disorder or disease, and/or the prophylactic or therapeutic effect may or may include other mechanisms in addition to inhibition of renin. Therefore "dependent" has to be read as "dependent inter alia", (especially in cases where a disease or disorder is really exclusively dependent only on renin) preferably as "dependent mainly", more preferably as "dependent essentially only". A disease dependent on (especially inappropriate) activity of renin may also be one that simply responds to modulation of renin activity, especially responding in a beneficial way (e.g. lowering the blood pressure) in case of renin inhibition.

Where a disease or disorder dependent on inappropriate activity of a renin is mentioned (such in the definition of "use" in the following paragraph and also especially where a compound of the formula I is mentioned for use in the diagnostic or therapeutic treatment which is preferably the treatment of a disease or disorder dependent on inappropriate renin activity, this refers preferably to any one or more diseases or disorders that depend on inappropriate activity of natural renin and/or one or more altered or mutated forms thereof.

Where subsequently or above the term "use" is mentioned (as verb or noun) (relating to the use of a compound of the formula I or of a pharmaceutically acceptable salt thereof, or a method of use thereof), this (if not indicated differently or to be read differently in the context) includes any one or more of the following embodiments of the invention, respectively (if not stated otherwise): the use in the treatment of a disease or disorder that depends on (especially inappropriate) activity of renin, the use for the manufacture of pharmaceutical compositions for use in the treatment of a disease or disorder that depends on (especially inappropriate) activity of renin; a method of use of one or more compounds of the formula I in the treatment of a disease or disorder that depends on (especially inappropriate) activity of renin; a pharmaceutical preparation comprising one or more compounds of the formula I for the treatment of a disease or disorder that depends on (especially inappropriate) activity of renin; and one or more compounds of the formula I for use in the treatment of a disease or disorder in a warm-blooded animal, especially a human, preferably a disease that depends on (especially inappropriate) activity of renin; as appropriate and expedient, if not stated otherwise.

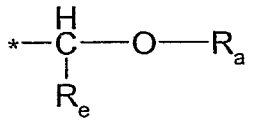
The terms "treat", "treatment" or "therapy" refer to the prophylactic (e.g. delaying or preventing the onset of a disease or disorder) or preferably therapeutic (including but not limited to preventive, delay of onset and/or progression, palliative, curing, symptom-alleviating, symptom-reducing, patient condition ameliorating, renin-modulating and/or renin-inhibiting) treatment of said disease(s) or disorder(s), especially of the one or more diseases or disorders mentioned above or below.

Preferred embodiments according to the invention

The groups of preferred embodiments of the invention mentionedin the claims and below are not to be regarded as exclusive, rather, e.g., in order to replace general expressions or symbols with more specific definitions, parts of those groups of compounds can be interchanged or exchanged using the definitions given above, or omitted, as appropriate, and each of the more specific definitions, independent of any others, may be introduced independently of or together with one or more other more specific definitions for other more general expressions or symbols.

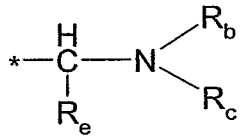
In a first preferred embodiment, the invention relates to a compound of the formula I wherein
R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;
R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, substituted monocyclic or (preferably) unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl or substituted or unsubstituted alkynyl; with the proviso that if R^1 is one of the moieties mentioned in the definition of R^1 other than acyl then R^2 can also be unsubstituted (or substituted) monocyclic aryl-alkyl (meaning that in addition to the group of other moieties mentioned in the definition of R^2, the substituent R^2 can also be selected from unsubstituted monocyclic aryl-alkyl);
R^3 is a moiety selected from the group of moieties of the formulae

(a)

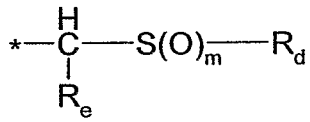


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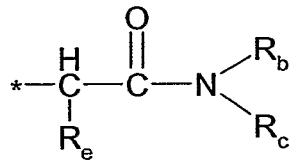
(b)



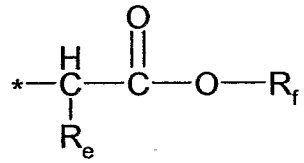
(c)



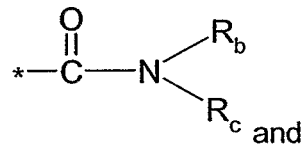
(d)



(e)

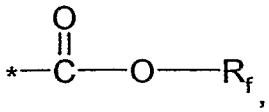


(f)



and

(g)



,

where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted

mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen, with the proviso that preferably not more than one of R_b and R_c is acyl, and with the proviso that if R_c is one of the mentioned moieties other than acyl (meaning here and hereinafter that R_c is one of the moieties mentioned for R_b and R_c except for acyl, especially R_c = hydrogen or C_1-C_7-alkyl) then R_b can (as additional alternative to the other mentioned moieties) also be unsubstituted or substituted monocyclic aryl-alkyl;

Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (preferably if m is 0) acyl, or can have one of these meanings or can be -N(R_b)(R_c) if m is 1 or preferably 2;

R_e is hydrogen, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl; and

R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;

m is 0, 1 or 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;

and T is methylene (-CH_2-) (preferred), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-), carbonyl (-C(=O)-) (preferred) or thiocarbonyl (-C(=S)-);

or a pharmaceutically acceptable salt thereof,

for use in the (therapeutic or prophylactic) treatment of a mammal, especially a human, preferably of a disease that depends on the activity of renin, especially a disease that responds to inhibition of renin in a beneficial way, most preferably hypertension.

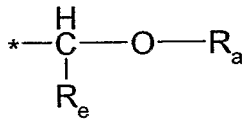
Regarding new compounds, the invention especially, in a still more preferred embodiment, relates to a compound of the formula I wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that if R^1 is one of the moieties mentioned in the definition of R^1 other than acyl then R^2 can also be unsubstituted or substituted monocyclic aryl-alkyl (meaning that in addition to the group of other moieties mentioned in the definition of R^2, the substituent R^2 can also be selected from unsubstituted monocyclic aryl-alkyl); ;

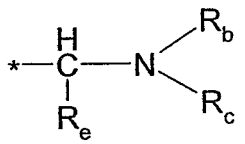
R^3 is a moiety selected from the group of moieties of the formulae

(a)

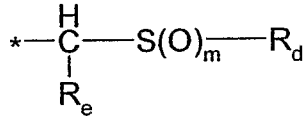


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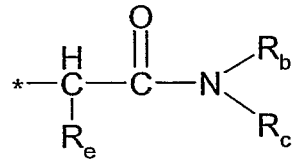
(b)



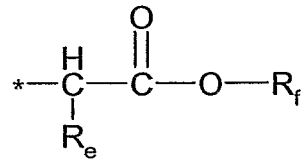
(c)



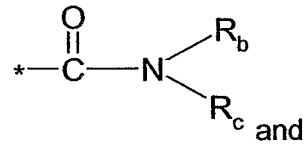
(d)



(e)

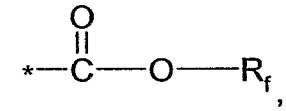


(f)



and

(g)



where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen, with the proviso that preferably not more than one of R_b and R_c is acyl, and with the proviso that if R_c is one of the mentioned (in the definition of R_c in this paragraph) moieties other than acyl then R_b can also be unsubstituted or substituted monocyclic aryl-alkyl;

Rd in a moiety of the formulae (c) or (e) is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (preferably if m is 0) acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;

R_e is hydrogen (preferred), unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl; and

R_f is substituted alkyl or preferably unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;

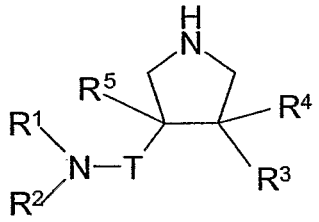
m is 0, 1 or 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;

and T is methylene ($-CH_2-$) (preferred), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-), carbonyl (-C(=O)-) (preferred) or thiocarbonyl (-C(=S)-);

or a (preferably pharmaceutically acceptable) salt thereof.

A compound of the formula I as such



(I)

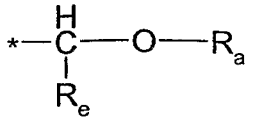
wherein

R^1 is acyl;

R^2 is unsubstituted or substituted alkyl,

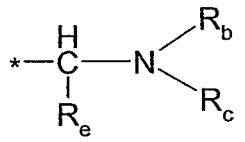
R^3 is a moiety selected from the group of moieties of the formulae

(a)

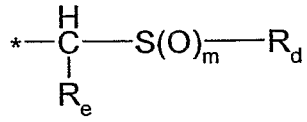


;

(b)

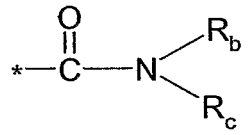


(c)



and

(f)



where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I, more preferably selected from the moieties of the formula (a), (b) or (f);

R_a is acyl or hydrogen;

R_b is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl or acyl;

R_c is hydrogen, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl or preferably C_3-C_8-cycloalkyl or C_1-C_7-alkyl;

R_d is unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl or -$N(R_b)(R_c)$;

R_e is hydrogen or C_1-C_7-alkyl; and

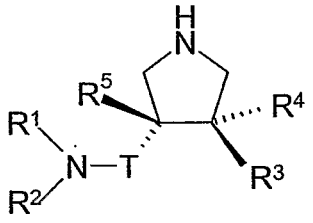
m is 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy; where preferably at least one, more preferably both of R^4 and R^5 are hydrogen;

and T is methylene (-CH_2-) (preferred), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-), carbonyl (-C(=O)-) (preferred) or thiocarbonyl (-C(=S)-);

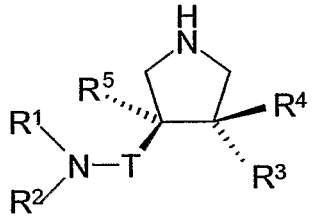
or an (especially pharmaceutically acceptable) salt thereof, is one further preferred embodiment of the invention.

Highly preferably, a compound of the formula I in the preceding and subsequent embodiments (be it use, compound for use or new compound) is of the formula IA with the following configuration:



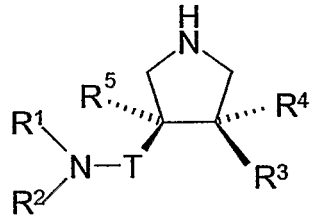
(IA);

Alternatively and defining a still preferred embodiment of the invention; a compound of the formula I in the preceding and subsequent embodiments (be it use, compound for use or new compound) can be of the formula IB with the following configuration:



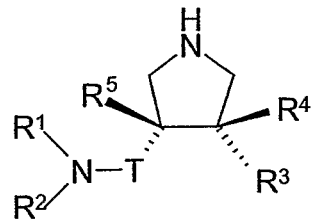
(IB)

Alternatively and defining a still preferred embodiment of the invention, a compound of the formula I in the preceding and subsequent embodiments (be it use, compound for use or new compound) can be of the formula IC with the following configuration:



(IC)

Alternatively and defining a still preferred embodiment of the invention; a compound of the formula I in the preceding and subsequent embodiments (be it use, compound for use or new compound) can be of the formula ID with the following configuration:



(ID)

In each of the formulae IA, IB, IC and ID, the moieties R^1, R^2, R^3, R^4, R^5 and L are as defined hereinbefore or preferably hereinafter for the respective more general or especially more preferred embodiments of the invention.

The formula IA, IB, IC or ID can replace formula I wherever a compound of the formula I (including a salt thereof) is mentioned hereinbefore or hereinafter; also, the corresponding intermediates are preferred.

A further preferred embodiment of the invention relates to the use of a compound of the formula I wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;
R^2 is unsubstituted or substituted mono- or bicyclic aryl-alkyl;
R^3 is a moiety selected from the group of moieties of the formulae (a), (b), (c), (d), (e), (f) or (g), more preferably of the formulae (a), (b), (c) and (f), still more preferably of the formulae (a), (b) or (f), given in the first description of a compound of the formula I in this disclosure; where in any of the moieties of these moiety formulae the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,
R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;
R_b and R_c are independently selected from the moieties given under R_a, with the proviso that preferably not more than one of R_b and R_c is acyl,
Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono-

or bicyclic cycloalkyl-alkyl or (preferably if m is 0) acyl, or can have one of these meanings or can be -N(R_b)(R_c) if m is 1 or preferably 2;
R_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl or hydrogen; and
R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;
m is 0, 1 or 2, preferably 0 or more preferably 2;
each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;
and T is methylene (-CH_2-), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-) , carbonyl (-C(=O)-) or thiocarbonyl (-C(=S)-);
or a pharmaceutically acceptable salt thereof,
in the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin, especially hypertension; or in the treatment of a disease that depends on activity of renin, especially hypertension.

Another preferred embodiment of the invention relates to the use of a compound of the formula I, wherein, R^1 is phenyl, naphthyl, mono- or bicyclic heterocyclyl, phenylcarbonyl, phenylacetyl, naphthylcarbonyl, naphthylacetyl, mono- or bicyclic heterocyclylcarbonyl or -acetyl, phenylsulfonyl, naphthylsulfonyl or mono- or bicyclic heterocyclylsulfonyl; wherein mono- or bicyclic heterocyclyl is pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazolyl, benzofuranyl, benzothiophenyl, or more preferably isoquinolyl, quinolyl or especially indolyl, and each such mono- or bicyclic heterocyclyl, phenyl or naphthyl mentioned under R^1 is unsubstituted or preferably substituted by one or more, especially one to three, moieties, preferably independently selected from the group consisting of
(i) a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H (especially in substituted aryl or substituted aryl-alkyl as R^1) where C_0-alkylene means that a

bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or (with lower preference) substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkanoyl, naphthyl-C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; e.g. C_1-C_7-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, such as 3-methoxypropyl or 2-methoxyethyl, C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyloxy- or naphthyloxy-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, such as aminomethyl, C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl, mono- or di- (C_1-C_7-alkyl-, naphthyl-, phenyl, naphthyl-C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-O-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-SO_2-NH-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyloxy, halo-C_1-C_7-alkylthio, such as trifluoromethylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, mono- or di-(C_1-C_7-alkyl-, naphthyl-C_1-C_7-alkyl-, phenyl-C_1-C_7-alkyl- and/or C_1-C_7-alkoxy-C_1-C_7-alkyl-)amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkanoylamino, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyl-amino, carboxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkoxycarbonyl, amino-C_1-C_7-alkoxycarbonyl, (N-) mono-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkoxycarbonyl, N- mono- or N,N-di-(C_1-C_7-alkyl, naphthyl-C_1-C_7.alkyl and/ or phenyl-C_1-C_7-alkyl)-aminocarbonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, amino-C_1-C_7-alkylsulfonyl, N-mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylsulfonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylsulfonyl, N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl or N-mono- or N,N-di-(C_1-C_7-alkyl)-aminosulfonyl,

(ii) from C_2-C_7-alkenyl, C_2-C_7-alkynyl, phenyl, naphtyl, mono- or bicyclic heterocyclyl, especially as defined below for mono- or bicyclic heterocyclyl, preferably selected from pyrrolyl, furanyl, thienyl, pyrimidine-2,4-dione-1-, -3- or –5-yl, tetrahydropyranyl and tetrahydrofuranyl, phenyl- or naphthyl- or (mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl or C_1-C_7-alkyloxy wherein mono- or bicyclic heterocyclyl is as defined below, preferably selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl; such as benzyl or naphthylmethyl, tetrahydrofuranyl- or tetrahydropyranyl-C_1-C_7-alkyloxycarbonyl, benzoyl- or naphthoylamino-C_1-C_7-alkyl, (phenyl- or naphthyl- or mono- or bicyclic heterocyclyl)-sulfonylamino-C_1-C_7-alkyl wherein phenyl or naphthyl or mono- or bicyclic heterocyclyl is unsubstituted or substituted, preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, halo, hydroxy, phenyl-C_1-C_7-alkoxy wherein phenyl is preferably unsubstituted or substituted, preferably by C_1-C_7-alkoxy and/or halo, mono- or bicyclic heterocyclyl-C_1-C_7-alkoxy, (mono- or bicyclic heterocyclyl or phenyl or naphthyl)-oxy, naphthyl-C_1-C_7-alkyloxy, benzoyl or naphthoyl or mono- or bicyclic heterocyclylcarbonyl)-oxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)- aminocarbonyloxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-thio, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-thio, nitro, amino, di-((naphthyl or phenyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl)-amino, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-amino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxycarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyloxycarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, amino-C_1-C_7-alkylcarbonyl, (N-) mono- or (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylcarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxy-carbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkoxycarbonyl, (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono or N,N-di-(naphthyl or phenyl or mono- or bicyclic heterocyclyl)-aminocarbonyl, cyano, C_1-C_7-alkylene which is unsubstituted or substituted by up to four C_1-C_7-alkyl substituents and bound to two adjacent ring atoms of the aryl moiety, sulfenyl, sulfinyl, C_1-C_7-alkylsulfinyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfinyl wherein phenyl or naphthyl is unsubstituted or

substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, mono- or bicyclic heterocyclyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl-C_1-C_7-alkyl)-aminosulfonyl;

where any phenyl or naphthyl or mono- or bicyclic heterocyclyl - which mono- or bicyclic heterocyclyl is preferably as defined for mono- or bicyclic heterocyclyl, more preferably is selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl - mentioned as substituent of or as part of a substituent of mono- or bicyclic heterocyclyl, phenyl or naphthyl R^1 under (i) or (ii) is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, halo, especially fluoro, chloro, bromo or iodo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents;

R^2 is phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl, wherein each phenyl or naphthyl mentioned so far in the definition of R^2 is unsubstituted or substituted as just described for substituted phenyl or naphthyl in the definition of R^1,

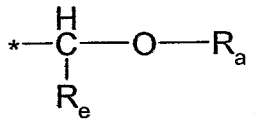
or is preferably C_1-C_7-alkyl that is unsubstituted or substituted by one or more, especially up to three, e.g. one or two, substituents independently selected from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, C_1-C_7-alkanoyloxy, (C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonyloxy, benzoyl- or

naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, such as trifluoromethylthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, benzoyl- or naphthoylamino, phenyl- or naphthyl-C_1-C_7-alkylcarbonylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl (-S-OH), sulfonyl (-S(=O)-OH), C_1-C_7-alkylsulfinyl (C_1-C_7-alkyl-S(=O)-), phenyl- or naphthylsulfinyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonylamino or –aminocarbonyloxy and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino;

or C_3-C_{10}-cycloalkyl or C_3-C_{10}-cycloalkyl-C_1-C_7-alkyl;

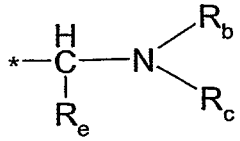
R^3 is a moiety selected from the group of moieties of the formulae

(a)

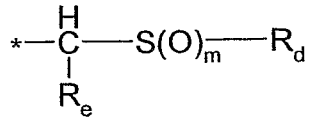


;

(b)

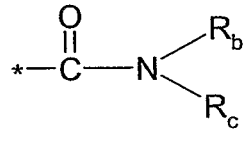


(c)



and

(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is acyl selected from the group consisting of C_1-C_7-alkanoyl, such as acetyl, 3,3-dimethyl-butyryl, 2,2-dimethyl-propionyl or 3,3-dimethyl-butyryl, unsubstituted (or with lower preference) mono-, di- or tri-(halo C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted) phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkylcarbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclohexylacetyl or cyclohexylcarbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, such as tetrahydrofuranyl-carbonyl, tetrahydropyranylcarbonyl, tetrahydrofuranylacetyl or tetrahydropyranylacetyl, , N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl (e.g. benzyl)]-aminocarbonyl, N-[C_3-C_8-cycloalkyl (e.g. cyclohexyl-) or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]aminocarbonyl, C_1-C_7-alkylaminocarbonyl, or (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or napthyl-C_1-C_7-alkyl)-oxycarbonyl, e.g. C_1-C_7-alkoxycarbonyl, such as tert-butyloxycarbonyl or isobutyloxycarbonyl, or phenyl-C_1-C_7-alkyloxycarbonyl; or is hydrogen;

R_b is C_1-C_7-alkyl or – in each case unsubstituted or substituted - phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from the group consisting of C_1-C_7-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, C_2-C_7-alkenyl, C_2-C_7-alkinyl, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, such as 3-methoxypropyl or 2-methoxyethyl, amino-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, C_1-C_7-alkoxy-carbonyl, carboxy-C_1-C_7-alkyl, halo, hydroxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, halo-C_1-C_7-alkylthio, such as trifluoromethylthio, nitro, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-

alkoxy-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, carbamoyl, cyano, C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl) -aminosulfonyl; or is acyl as just defined under R_a or selected from unsubstituted or mono-, di- or tri-(halo and/or C_1-C_7alkyl)-substituted (phenyl or phenyl-C_1-C_7-alkyl)-sulfonyl, such as phenylsulfonyl or phenylmethanesulfonyl, or C_1-C_7-alkylsulfonyl, such as methanesulfonyl;
R_c is hydrogen, C_1-C_7-alkyl, C_3-C_8-cycloalkyl, hydroxy-C_1-C_7-alkyl or C_1-C_7-alkyloxy-C_1-C_7-alkyl, preferably hydrogen or C_1-C_7-alkyl;
R_d is unsubstituted or substituted phenyl- or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from those mentioned for unsubstituted of substituted phenyl- or naphthyl-C_1-C_7-alkyl under R_b, or is -N(R_b)(R_c);
R_e is C_1-C_7-alkyl or preferably hydrogen; and
m is 2;

each of R^4 and R^5 is selected, independently from the other, from C_1-C_7-alkyl, hydroxy, C_1-C_7-alkyloxy and preferably hydrogen;
and T is carbonyl or preferably methylene;

or a pharmaceutically acceptable salt thereof, for the treatment of a disease that depends on activity of renin, especially hypertension, or preferably for the manufacture of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin, especially hypertension.

A quite preferred embodiment of the invention relates to a new compound of the formula I, wherein
R^1, R^3, R^4, R^5, m and T are as defined in the preceding paragraph and
R^2 is phenyl, naphthyl or (with lower preference) naphthyl-C_1-C_7-alkyl, wherein each phenyl or naphthyl mentioned so far in the definition of R^2 is unsubstituted or substituted as just described for substituted phenyl or naphthyl in the definition of R^1, or preferably C_1-C_7-alkyl that is unsubstituted or substituted by one or more, especially up to three, e.g. one or two, substituents independently selected from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-

alkyloxy, C_1-C_7-alkanoyloxy, benzoyl- or naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, such as trifluoromethylthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, C_1-C_7-alkanoylthio, benzoyl- or naphthoylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, mono- or di-(naphthyl- or phenyl-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, benzoyl- or naphthoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl, (-S-OH) sulfonyl (-S(=O)-OH), C_1-C_7-alkylsulfinyl (C_1-C_7-alkyl-S(=O)-), phenyl- or naphthylsulfinyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-aminocarbonylamino and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino; or is C_3-C_{10}-cycloalkyl or C_3-C_{10}-cycloalkyl-C_1-C_7-alkyl;

or a (preferably pharmaceutically acceptable) salt thereof.

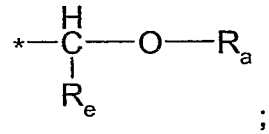
In another very preferred embodiment, the invention relates to a new compound of the formula I wherein

R^1 is phenyl-, indolyl- or quinolyl-C_1-C_7-alkanoyl (preferably –carbonyl or –acetyl) wherein the phenyl, indolyl or quinolyl is substituted by C_1-C_7-alkyloxy-C_1-C_7-alkyloxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl or C_1-C_7-alkyloxy-C_1-C_7-alkyloxy-C_1-C_7-alkyland may further be substituted by one or more, e.g. up to three, C_1-C_7-alkyl (especially methyl) and/or C_1-C_7-alkyloxy moieties;

R^2 is C_1-C_7-alkyl;

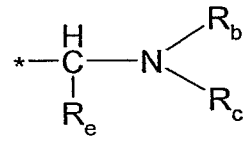
R^3 is a moiety selected from the group of moieties of the formulae

(a)

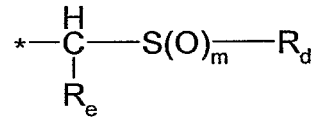


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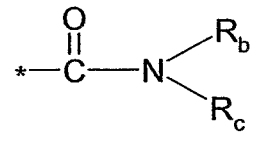
(b)



(c)



(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

wherein

R_a is hydrogen or N-mono- or N,N-di-(C_1-C_7-alkyl, (unsubstituted or halo-substituted) phenyl or naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl or C_3-C_8-cycloalkyl)-aminocarbonyl;

each of R_b and R_c is, independently of the other, selected from hydrogen, C_1-C_7-alkyl, phenyl, naphthyl, naphthyl-C_1-C_7-alkyl, C_3-C_8-cycloalkylcarbonyl (= C_3-C_8-cycloalkyl-C(=O)-), , C_3-C_8cycloalkyl-C_1-C_7-alkylcarbonyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted phenyl- or naphthyl-C_1-C_7-alkanoyl, preferably benzoyl or phenylacetyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, such as tetrahydrofuranyl-carbonyl, tetrahydropyranylcarbonyl, tetrahydrofuranylacetyl or tetrahydropyranylacetyl, C_1-C_7-alkylsulfonyl (= C_1-C_7-alkanesulfonyl) or (unsubstituted or [C_1-C_7-alkyl-, halo-lower alkyl-, halo, C_1-C_7-alkyloxy-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted) (phenyl- or naphthyl)-C_1-C_7-alkylsulfonyl, with the proviso that if R_c is hydrogen, C_1-C_7-alkyl, phenyl, naphthyl or naphthyl-C_1-C_7-alkyl, then R_b can also be phenyl-C_1-C_7-alkyl; R_d is unsubstituted or [C_1-C_7-alkyl-, phenyl-, halo-lower alkyl-, halo, oxo-C_1-C_7-alkyl-, C_1-C_7-alkyloxy-, phenyl-C_1-C_7-alkoxy-, halo-C_1-C_7-alkyloxy-, phenoxy-, C_1-C_7-

alkanoylamino-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted (phenyl- or naphthyl)-C_1-C_7-alkyl;
R_e is hydrogen; and
m is 2;

each of R^4 and R^5 is hydrogen; and
T is carbonyl or preferably methylene;

or a (preferably pharmaceutically acceptable) salt thereof.

In the following, preferred definitions are provided individually for each variant. It should be noted that each of the preferred definitions for any variant can be combined with any preferred definition of another variant(s).

Preferred definitions for R^1

R^1 is as defined in the claims, preferably R^1 is acyl as defined herein, more preferably bearing a carbonyl group.

In a first embodiment R^1 is unsubstituted or substituted aryl-carbonyl.
Preferred examples for the aryl moiety of the acyl substituent are phenyl and naphthyl, more preferably phenyl. When the aryl moiety is substituted, it is preferably preferably mono-, di- or tri-substituted, more preferably di-substituted. Suitable substituents for the aryl moiety are as defined herein, preferably -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H, wherein r and s are 0 or 1 and Y and X are independently O , NH or NH-CO-O-; or is halo, such as Cl or F, hydroxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, monocyclic heterocyclyl-C_1-C_7-alkyloxy, wherein heterocyclyl is preferably a 5- or 6-membered ring containing a nitrogen atom, such as isoxazolyl; nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H, monocyclic heterocyclyl-C_1-C_7-alkyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy or halo. When the alkylene moieties of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H are substituted, they are preferably substituted by one or more, more preferably three halo such as F. Preferred examples of -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H include –(O or NH, preferably O)-C_1-C_7-alkyl, -C_1-C_7-alkyl, -

(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, -(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-H, -C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, -C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, –(O or NH, preferably O)-halo-C_1-C_7-alkyl, or -(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-halo-C_1-C_7-alkyl, most preferably -OMe, -OC_3H_6OMe, methyl, ethyl, t-butyl, -$CH_2OC_2H_4OMe$, -$OC_2H_4OC_2H_4$, -OC_3H_6OH, -C_4H_8OMe, -CHF_2, -OCF_3, -$OC_2H_4CF_3$, -$OC_3H_6CF_3$, and -$OC_3H_6OCF_3$. In preferred embodiments, the aryl moiety is di-substituted whereby both substituents are -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H as defined herein, more preferably one substituent is –O-C_1-C_7-alkyl, such as OMe, or -C_1-C_7-alkyl, such as methyl or ethyl, and the other is -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, such as -OC_3H_6OMe.

In a second embodiment R^1 is unsubstituted or substituted heterocyclyl-carbonyl.
Preferred examples for the heterocyclyl moiety of the acyl substituent are mono- or bicyclic, preferably bicyclic, heterocyclyl. Preferred are aromatic ring systems, or in particular if a bicyclic moiety is contemplated, partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated. Most preferred are aromatic ring systems. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more preferably O or N. Particularly preferred examples include pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, benzopyrazolyl, benzo[1,2,5]oxadiazolyl, and 3,4-dihydro-2H-benzo[1,4]dioxinyl, or more preferably indolyl, isoquinolyl, quinolyl and 3,4-dihydro-2H-benzo[1,4] dioxinyl or especially indolyl, and 3,4-dihydro-2H-benzo[1,4] dioxinyl. When the heterocyclyl moiety is substituted, it is preferably mono- or di-substituted, most preferably di-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H, wherein r and s are 0 or 1 and Y and X are independently O , NH or NH-CO-O-, halo-C_1-C_7-alkyl, halo, hydroxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano. Preferred examples of -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H include –(O or NH, preferably O)-C_1-C_7-alkyl, -C_1-C_7-alkyl, -(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, -(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-H, -C_1-C_7-

alkylene-(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, -C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, more preferably -C_1-C_7-alkyl, -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, or -C_1-C_7-alkylene-O-C_1-C_7-alkyl, still more preferably methyl, ethyl, -C_2H_4-NH-CO-OMe, -$CH_2OC_2H_4OMe$, -$OC_2H_4OC_2H_4$, -OC_3H_6OH, -C_2H_4OMe, -C_3H_6OMe and –NH-C_3H_6OMe, yet more preferably - methyl, -OC_3H_6OMe and -C_3H_6OMe. Most preferably the heterocyclyl moiety is substituted by methyl and/or -C_3H_6OMe.

Preferred definitions for R^2

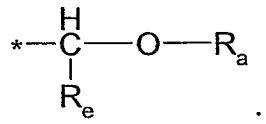
R^2 is as defined in the claims, preferably R^2 is in a first embodiment unsubstituted or substituted alkyl as defined herein. Preferred examples are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted. In a preferrred embodiment, R^2 is branched alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, and 1,2-dimethyl-propyl, most preferably isopropyl. Branched alkyl is preferably unsubstituted. If the alkyl moiety is substituted, suitable substituents are as defined herein, preferably O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano.

Preferably in a second embodiment R^2 is cycloalkyl. Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_3, C_4, C_5 and C_6-cycloalkyl, most preferably cyclopropyl. The cycloalkyl moiety may be substituted or unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, most preferably phenyl or naphthyl. Most preferably, the cycloalkyl moiety is unsubstituted.

Preferred definitions for R^3

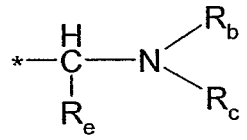
R^3 is as defined in the claims, preferably R^3 is a moiety selected from the group of moieties of the formulae

(a)

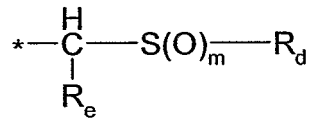


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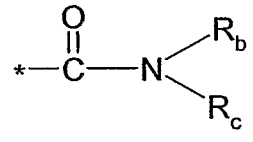
(b)



(c)



(f)



and

more preferably (a), (b) or (f), still more preferably (a) or (b), most preferably (b), where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I, wherein

R_a is acyl selected from C_1-C_7-alkanoyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted) phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkylcarbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]-aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl; or is hydrogen;

R_b is C_1-C_7-alkyl or – in each case unsubstituted or substituted - phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from the group

consisting of C_1-C_7-alkyl, C_2-C_7-alkenyl, C_2-C_7-alkinyl, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, C_1-C_7-alkoxy-carbonyl, carboxy-C_1-C_7-alkyl, halo, hydroxy, halo-C_1-C_7-alkoxy, halo-C_1-C_7-alkylthio, nitro, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, carbamoyl, cyano, C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl) -aminosulfonyl; or is acyl as just defined under R_a or selected from unsubstituted mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, C_1-C_7-alkylsulfonyl;

R_c is, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl, unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, or preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or unsubstituted or substituted C_1-C_7-alkyl;

R_d is unsubstituted or substituted phenyl- or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from those mentioned for unsubstituted of substituted phenyl- or naphthyl-C_1-C_7-alkyl under R_b , or is -N(R_b)(R_c);

R_e is C_1-C_7-alkyl or preferably hydrogen; and

m is 2;

preferably R_a is hydrogen or N-mono- or N,N-di-(C_1-C_7-alkyl, (unsubstituted or halo-substituted) phenyl or naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl C_3-C_8-cycloalkyl-C_1-C_7-alkyl, heterocyclyl-C_1-C_7-alkyl, heterocyclyl and/or C_3-C_8-cycloalkyl)-aminocarbonyl;

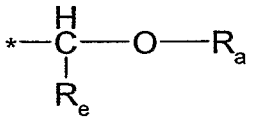
each of R_b and R_c is, independently of the other, is selected from hydrogen, C_1-C_7-alkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, unsubstituted or substituted aryl such as phenyl, naphthyl, naphthyl-C_1-C_7-alkyl, or acyl such as C_3-C_8-cycloalkylcarbonyl, C_3-C_8cycloalkyl-C_1-C_7-alkylcarbonyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted phenyl- or naphthyl-C_1-C_7-alkanoyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, C_1-C_7-alkylsulfonyl or (unsubstituted or [C_1-C_7-alkyl-, halo-lower alkyl-, halo, C_1-C_7-alkyloxy-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted) (phenyl- or naphthyl)-C_1-C_7-alkylsulfonyl, with the proviso that if R_c is hydrogen, C_1-C_7-alkyl, phenyl, naphthyl or naphthyl-C_1-C_7-alkyl, then R_b can also be phenyl-C_1-C_7-alkyl;

R_d is unsubstituted or [C_1-C_7-alkyl-, phenyl-, halo-lower alkyl-, halo, oxo-C_1-C_7-alkyl-, C_1-C_7-alkyloxy-, phenyl-C_1-C_7-alkoxy-, halo-C_1-C_7-alkyloxy-, phenoxy-, C_1-C_7-alkanoylamino-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted (phenyl- or naphthyl)-C_1-C_7-alkyl;

R_e is hydrogen; and

m is 2.

R^3 is in a first embodiment a moiety of the formula (a)



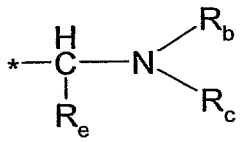
In this embodiment, R_a is as defined herein, preferably, R_a is hydrogen or acyl, preferably acyl. Acyl is preferably selected from C_1-C_7-alkanoyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted) phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkylcarbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, and (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or napthyl-C_1-C_7-alkyl)-oxycarbonyl, or preferably from N-mono- or N,N-di-substituted aminocarbonyl, in particular N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, such as N,N-di-(CH_2CHCH_3)-aminocarbonyl or N-(CH_2CHCH_3)(methyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl, such as phenyl–CH_2- or as phenyl–$CH(CH_2CH_3)$-]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]-aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, such as N-(phenyl–CH_2-)(methyl or ethyl)aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, such as N-(phenyl–CH_2-)(cyclopropyl-CH_2-)aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, such as N-(methyl)(cyclohexyl-CH_2-)aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, such as N-(phenyl–CH_2-) (cyclopropyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, such as N-(heterocyclyl-C_1-C_7-alkyl)(cyclopropyl)-aminocarbonyl and N-(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, such as N-(heterocyclyl)(cyclopropyl)-aminocarbonyl, whereby heterocyclyl is in each instance preferably a monocyclic, such as 5- or 6- membered monocyclic, preferaby saturated ring systems or aromatic ring systems, in particular saturated ring systems. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more preferably O or N. Particularly preferred examples include 5- or 6-

membered rings preferably containing an oxygen atom, in particular tetrahydropyranyl or tetrahydrofuranyl. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably phenyl-C_1-C_7-alkyl,. Suitable phenyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted.

In this embodiment, R_e is as defined herein, preferably, R_e is hydrogen.

When R^3 is a moiety of the formula (a), then one or more, preferably all of the following substituents have the following definition:
R^1 is substituted phenyl carbonyl as defined herein, in particular whereby one substituent is –O-C_1-C_7-alkyl, such as OMe, or -C_1-C_7-alkyl, such as methyl or ethyl, and the other is -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, such as -OC_3H_6OMe; or R^1 is substituted aromatic heterocyclylcarbonyl, in particular bicyclic heterocyclylcarbonyl, such as indolyl-carbonyl, whereby the heterocyclyl moiety is substituted by methyl and/or -C_3H_6OMe;
R^2 is branched alkyl, such as isopropyl;
T is methylene, and
R^4 and R^5 are hydrogen.

R^3 is in a second embodiment a moiety of the formula (b)



In this embodiment, R_b is as defined herein, preferably R_b is selected from hydrogen, C_1-C_7-alkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, unsubstituted or substituted aryl such as phenyl, naphthyl, naphthyl-C_1-C_7-alkyl, or acyl, more preferably unsubstituted or substituted aryl or acyl, most preferably acyl, each as defined herein.

When R_b is unsubstituted or substituted aryl, preferred examples are phenyl or naphthyl, more preferably phenyl, which are each unsubstituted or substituted by a suitable substituent such as C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxy, phenyl- or naphthyloxy,

phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano; preferably each are unsubstituted.

When R_b is acyl, preferred examples are selected from the group consisting of (a) to (p), most preferably (e):

(a) Unsubstituted or substituted mono- or bicyclic aryl-carbonyl
Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl, indanyl, or 1,2,3,4-tetrahydronaphthyl. When the aryl moiety is substituted, it is preferably mono- or di-substituted. In particular, phenyl is preferably unsubstituted, mono- or di-substituted, and indanyl or 1,2,3,4-tetrahydronaphthyl are preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, unsubstituted or substituted, preferably unsubstituted, heterocyclyl or unsubstituted or substituted, preferably unsubstituted, heterocyclyl-C_1-C_4-alkyl, such as heterocyclyl-CH_2, whereby the heterocyclyl moiety in each case is preferably monocyclic 5- or 6-membered heterocyclyl, preferably containing an N and/or O atom, such as tetrahydrofuranyl or tetrahydropyranyl, piperidinyl, pyrrolidinyl, piperazinyl or morpholinyl, most preferably heterocyclyl, heterocyclyl-CH_2, -O-C_1-C_7-alkyl, -O-C_1-C_7-alkylene-O-alkyl and/or halo.

(b) unsubstituted or substituted mono- or bicyclic heterocyclylcarbonyl
Preferred examples for the heterocyclyl moiety are mono- or bicyclic rings. Preferred are 3 to 14, more preferably 5 to 11 membered ring systems. The heterocyclyl moiety may be saturated, partially saturated or aromatic, in particular if a monocyclic moiety is contemplated, aromatic or saturated rings, or, in particular if a bicyclic moiety is contemplated, aromatic or partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated or partially saturated. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more

preferably O or N. Particularly preferred examples include 5- or 6-membered rings preferably containing a nitrogen or an oxygen atom, in particular pyrrolidinyl, oxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, or tetrahydropyranyl; or 9- to 11-membered bicyclic ring systems preferably containing at least one nitrogen and/or oxygen atom, in particular indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, benzofuranyl, 4H-benzo[1,4]oxazin-3-onyl, benzooxazolyl, benzo[1,2,5]oxadiazolyl, benzimidazolyl or 3,4-dihydro-2H-benzo[1,4]oxazinyl, more preferably pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, tetrahydropyranyl, indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, or 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably phenyl, -C_1-C_7-alkyl or C_3-C_8-cycloalkyl. Suitable phenyl and cycloalkyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted or is mono-substituted with phenyl, -C_1-C_7-alkyl or C_3-C_8-cycloalkyl.

(c) unsubstituted or substituted mono- or bicyclic cycloalkylcarbonyl

Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_8-cycloalkyl, more preferably C_3, C_4, C_5, C_6 and C_7-cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted. C_3, C_4, C_5, and C_7-cycloalkyl are preferably unsubstituted and C_6-cycloalkyl is preferably unsubstituted or substituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted,

phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano, most preferably O-C_1-C_4-alkyl or hydroxy.

(d) unsubstituted or substituted alkylcarbonyl

Preferred examples for the alkyl moiety are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted. In one embodiment, the alkyl moiety is branched alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, most preferably isobutyl, isopentyl and 2,2-dimethyl-propyl. In another embodiment the alkyl moiety is straight chain alkyl such as methyl, ethyl, n-propyl, n-butyl or n-pentyl, preferably methyl, ethyl or n-propyl. Alkyl is preferably substituted. When the alkyl moiety is substituted, it is preferably mono-, di- or tri-substituted, more preferably mono-substituted. Suitable substituents for the alkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano, whereby suitable phenyl or naphthyl substituents include C_1-C_7-alkyl, such as methyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino, preferably C_1-C_7-alkyl, and whereby suitable amino substituents include C_1-C_7-alkyl, such as methyl, phenyl or cyclopropyl, preferably C_1-C_7-alkyl. Most preferably the alkyl moiety is mono-substituted by -O-C_1-C_7-alkyl, hydroxyl, C_1-C_7-alkanoylamino, unsubstituted or di-substituted phenyloxy, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl and C_1-C_7-alkyloxycarbonyl.

(e) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkylcarbonyl

Preferably aryl alkyl is aryl-C_{1-6} alkyl, more preferably aryl-C_{1-4} alkyl, in particular aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$C(CH_3)_2$-, most preferably aryl-CH_2-. The alkyl moiety, in particular when aryl alkyl is aryl-CH_2- or aryl-CH_2CH_2-, may be substituted, preferably mono-substituted. Examples of preferred substituents include O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano or unsubstituted or substituted, preferably unsubstituted, phenyl, whereby suitable phenyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-

alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino; most preferably unsubstituted phenyl, C_1-C_7-alkanoylamino, O-C_1-C_4-alkyl or hydroxyl.

Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl or naphthyl. When the aryl moiety is substituted, it is preferably mono-, di- or tri-substituted. In particular, phenyl is preferably unsubstituted, mono-, di- or tri-substituted, and naphthyl is preferably unsubstituted. In one embodiment, phenyl is preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably substituted, phenyl or naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano. Suitable substituents for the phenyl and naphthyl substituent on the aryl moiety of aryl alkylcarbonyl include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the aryl alkyl moiety is unsubstituted or substituted by -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, substituted phenyl, C_1-C_7-alkanoylamino and/or halo.

(f) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkylcarbonyl

Preferably heterocyclyl alkyl is heterocyclyl-C_{1-6} alkyl, more preferably heterocyclyl-C_{1-4} alkyl, in particular heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2C(CH_3)_2$-, most preferably heterocyclyl-CH_2-. Heterocyclyl-$CH_2C(CH_3)_2$- is particularly preferred when the heterocyclyl moiety is a 5- or 6-membered ring such as an aromatic ring, in particular pyrrolyl. Heterocyclyl-CH_2CH_2- is particularly preferred when the heterocyclyl moiety is a 5- or 6-membered ring such as an aromatic ring, in particular furanyl.

Preferred examples for the heterocyclyl moiety are mono- or bicyclic rings. Preferred are 3 to 14, more preferably 5 to 11 membered ring systems. The heterocyclyl moiety may be saturated, partially saturated or aromatic, in particular if a monocyclic moiety is contemplated, aromatic or saturated rings, or, in particular if a bicyclic moiety is contemplated, aromatic or partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated or partially saturated. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more

preferably O or N. Particularly preferred examples include 5- or 6-membered rings preferably containing a nitrogen or an oxygen atom, in particular pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, tetrahydrofuranyl, or tetrahydropyranyl; or 9- to 11-membered bicyclic ring systems preferably containing at least one nitrogen and/or oxygen atom, in particular 4H-benzo[1,4]oxazin-3-onyl, benzooxazolyl, indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, benzofuranyl, benzo[1,2,5]oxadiazolyl, benzimidazolyl or 3,4-dihydro-2H-benzo[1,4]oxazinyl, more preferably pyrrolidinyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl, 4H-benzo[1,4]oxazin-3-onyl or benzooxazolyl. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably -C_1-C_7-alkyl or C_1-C_7-alkanoyl. Suitable phenyl and cycloalkyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted or is mono-substituted with unsubstituted phenyl, -C_1-C_7-alkyl or C_1-C_7-alkanoyl.

(g) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkylcarbonyl

Preferably cycloalkyl alkyl is cycloalkyl-C_{1-6} alkyl, more preferably cycloalkyl-C_{1-4} alkyl, in particular cycloalkyl-CH_2-, cycloalkyl-CH_2CH_2- or cycloalkyl-$CH_2C(CH_3)_2$-, most preferably cycloalkyl-CH_2-. The alkyl moiety may be substituted, preferably mono-substituted, including on the carbon where the cycloalkyl moiety is attached. Examples of preferred substituents include O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, most preferably O-C_1-C_4-alkyl or hydroxyl. Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_3, C_5 and C_6-cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted. C_3-cycloalkyl is preferably unsubstituted and C_5 and C_6-cycloalkyl are preferably unsubstituted or substituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable

substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –NHCOCHCH$_3$)$_2$, carboxyl, and cyano, most preferably amino, O-C_1-C_4-alkyl or hydroxy.

(h) unsubstituted or substituted alkyloxycarbonyl

Preferred examples for the alkyl moiety are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted. In one embodiment, the alkyl moiety is branched alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, most preferably isobutyl, isopentyl and 2,2-dimethyl-propyl. In another embodiment the alkyl moiety is straight chain alkyl such as methyl, ethyl, n-propyl, n-butyl or n-pentyl, preferably methyl or ethyl. When the alkyl moiety is substituted, it is preferably mono-, di- or tri-substituted, more preferably mono-substituted. Suitable substituents for the alkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano, whereby suitable phenyl or naphthyl substituents include C_1-C_7-alkyl, such as methyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino, preferably C_1-C_7-alkyl, and whereby suitable amino substituents include C_1-C_7-alkyl, such as methyl, phenyl or cyclopropyl, preferably C_1-C_7-alkyl. Most preferably the alkyl moiety is mono-substituted by -O-C_1-C_7-alkyl, C_1-C_7-alkanoylamino and N-mono- or N,N-di-substituted aminocarbonyl.

(i) unsubstituted or substituted mono- or bicyclic aryl-oxycarbonyl

Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl or naphthyl. When the aryl moiety is substituted, it is preferably mono- or di-substituted. In particular, phenyl is preferably unsubstituted, mono- or di-substituted, and naphthyl is preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe,

halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, unsubstituted or substituted, preferably unsubstituted, heterocyclyl or unsubstituted or substituted, preferably unsubstituted, heterocyclyl-C_1-C_4-alkyl, such as heterocyclyl-CH_2, whereby the heterocyclyl moiety in each case is preferably monocyclic 5- or 6-membered heterocyclyl, preferably containing an N and/or O atom, such as tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl, pyrrolidin-2-onyl, piperazinyl or morpholinyl, most preferably heterocyclyl or -O-C_1-C_7-alkyl.

(j) unsubstituted or substituted mono- or bicyclic heterocyclyloxycarbonyl

Preferred examples for the heterocyclyl moiety are mono- or bicyclic rings. Preferred are 3 to 14, more preferably 5 to 11 membered ring systems. The heterocyclyl moiety may be saturated, partially saturated or aromatic, in particular if a monocyclic moiety is contemplated, aromatic or saturated, more preferably saturated, rings, or, in particular if a bicyclic moiety is contemplated, aromatic or partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated or partially saturated. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more preferably O or N. Particularly preferred examples include 5- or 6-membered rings preferably containing a nitrogen or an oxygen atom, in particular pyrrolidinyl, oxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, or tetrahydropyranyl; more preferably tetrahydrofuranyl or tetrahydropyranyl. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably phenyl, -C_1-C_7-alkyl or C_3-C_8-cycloalkyl. Suitable phenyl and cycloalkyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted.

(k) unsubstituted or substituted mono- or bicyclic cycloalkyloxycarbonyl

Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_8-cycloalkyl, more preferably C_3, C_4, C_5, C_6 and C_7-cycloalkyl, most preferably C_6-cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted, preferably unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano, most preferably O-C_1-C_4-alkyl or hydroxy.

(l) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyloxycarbonyl

Preferably aryl alkyl is aryl-C_{1-6} alkyl, more preferably aryl-C_{1-4} alkyl, in particular aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$CH(CH_2CH_3)$-, most preferably aryl-CH_2-. Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl. When the aryl moiety is substituted, it is preferably mono-, di- or tri-substituted. In one embodiment, phenyl is preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably substituted, phenyl or naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano. Suitable substituents for the phenyl and naphthyl substituent on the aryl moiety of aryl alkylcarbonyl include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino.

(m) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyloxycarbonyl

Preferably heterocyclyl alkyl is heterocyclyl-C_{1-6} alkyl, more preferably heterocyclyl-C_{1-4} alkyl, in particular heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2CH(CH_3)$-, most preferably heterocyclyl-CH_2-. Heterocyclyl-$CH_2CH(CH_3)$- is particularly preferred when the heterocyclyl moiety is a 5- or 6-membered ring such as a saturated ring, in particular 1,3-dioxane. Preferred examples for the heterocyclyl moiety are mono- or bicyclic rings.

Preferred are 3 to 14, more preferably 5 to 11 membered ring systems. The heterocyclyl moiety may be saturated, partially saturated or aromatic, in particular if a monocyclic moiety is contemplated, aromatic or saturated rings, or, in particular if a bicyclic moiety is contemplated, aromatic or partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated or partially saturated. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more preferably O or N. Particularly preferred examples include 5- or 6-membered rings preferably containing a nitrogen or an oxygen atom, in particular pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, 1,3-dioxane, tetrahydrofuranyl, or tetrahydropyranyl; more preferably pyridyl, piperidyl, isoxazolyl, tetrahydrofuranyl, tetrahydropyranyl or 1,3-dioxane. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, such as COMe, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably -C_1-C_7-alkyl or C_1-C_7-alkanoyl. Suitable phenyl and cycloalkyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted or is mono-substituted with -C_1-C_7-alkyl or C_1-C_7-alkanoyl.

(n) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyloxycarbonyl

Preferably cycloalkyl alkyl is cycloalkyl-C_{1-6} alkyl, more preferably cycloalkyl-C_{1-4} alkyl, in particular cycloalkyl-CH_2-, cycloalkyl-CH_2CH_2- or cycloalkyl-$CH_2CH(CH_3)$-, most preferably cycloalkyl-CH_2-. Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_3 and C_5 -cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted. C_3-cycloalkyl is preferably unsubstituted and C_5-cycloalkyl are preferably unsubstituted or substituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-

C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano, most preferably C_1-C_7-alkanoylamino.

(o) N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl

Preferred examples for the alkyl moiety of the unsubstituted or substituted alkyl aminocarbonyl are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted. In one embodiment, the alkyl moiety is branched alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, most preferably isopropyl or isobutyl. In another embodiment the alkyl moiety is straight chain alkyl such as methyl, ethyl, n-propyl, n-butyl or n-pentyl, preferably methyl or ethyl. When the alkyl moiety is substituted, it is preferably mono-, di- or tri-substituted, more preferably mono-substituted. Suitable substituents for the alkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano. Most preferably the alkyl moiety is unsubstituted.

Preferred examples of the aryl moiety of the unsubstituted or substituted aryl aminocarbonyl include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl or naphthyl. When the aryl moiety is substituted, it is preferably mono- or di-substituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-

C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano. Most preferably aryl is unsubstituted.

Preferred examples for the cycloalkyl moiety moiety of the unsubstituted or substituted cycloalkyl aminocarbonyl are monocyclic rings, preferably C_3-C_8-cycloalkyl, more preferably C_3, C_4, C_5, C_6 and C_7-cycloalkyl, most preferably C_3 or C_6-cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted, preferably unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano, most preferably O-C_1-C_4-alkyl or hydroxy.

Preferably the aryl alkyl moiety of the unsubstituted or substituted aryl alkyl aminocarbonyl is aryl-C_{1-6} alkyl, more preferably aryl-C_{1-4} alkyl, in particular aryl-CH_2-, aryl-CH_2CH_2-, or aryl-$CH(CH_2CH_3)$-, most preferably aryl-CH_2-. The alkyl moiety, in particular when aryl alkyl is aryl-CH_2-, may be substituted, preferably mono-substituted. Examples of preferred substituents include O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano or unsubstituted or substituted, preferably unsubstituted, phenyl, whereby suitable phenyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino; most preferred is unsubstituted phenyl. Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl. When the aryl moiety is substituted, it is preferably mono-, di- or tri-substituted. In one embodiment, phenyl is preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano, more preferably -O-C_1-C_7-alkyl or halo.

Preferably the heterocyclyl alkyl moiety of the unsubstituted or substituted heterocyclyl alkyl aminocarbonyl is heterocyclyl-C_{1-6} alkyl, more preferably heterocyclyl-C_{1-4} alkyl, in particular heterocyclyl-CH_2- or heterocyclyl-CH_2CH_2-, most preferably heterocyclyl-CH_2-. Preferred examples for the heterocyclyl moiety are mono- or bicyclic rings. Preferred are 3 to 14, more preferably 5 to 11 membered ring systems. The heterocyclyl moiety may be saturated, partially saturated or aromatic, in particular if a monocyclic moiety is contemplated, aromatic or saturated rings, or, in particular if a bicyclic moiety is contemplated, aromatic or partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated or partially saturated. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more preferably O or N. Particularly preferred examples include 5- or 6-membered rings preferably containing a nitrogen or an oxygen atom, in particular pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, 1,3-dioxane, tetrahydrofuranyl, or tetrahydropyranyl; more preferably furanyl or tetrahydropyranyl. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, such as COMe, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably -C_1-C_7-alkyl or C_1-C_7-alkanoyl. Suitable phenyl and cycloalkyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted.

Preferably the cycloalkyl alkyl moiety of the unsubstituted or substituted cycloalkyl alkyl aminocarbonyl is cycloalkyl-C_{1-6} alkyl, more preferably cycloalkyl-C_{1-4} alkyl, in particular cycloalkyl-CH_2-. Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_6 -cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted, preferably unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or

naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano, most preferably C_1-C_7-alkanoylamino.

Preferred examples of N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl include
(unsubstituted or substituted mono- or bicyclic aryl)(unsubstituted or substituted alkyl)aminocarbonyl,
unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl-aminocarbonyl,
unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl-aminocarbonyl,
unsubstituted or substituted mono- or bicyclic aryl-aminocarbonyl,
unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl-aminocarbonyl,
di-(unsubstituted or substituted mono- or bicyclic aryl)-aminocarbonyl,
di-(unsubstituted or substituted alkyl)-aminocarbonyl,
(unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl)(unsubstituted or substituted alkyl)-aminocarbonyl,
(unsubstituted or substituted mono- or bicyclic cycloalkyl)(unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl)-aminocarbonyl,
(unsubstituted or substituted mono- or bicyclic cycloalkyl)(unsubstituted or substituted mono- or bicyclic aryl)-aminocarbonyl, and
unsubstituted or substituted mono- or bicyclic cycloalkyl-aminocarbonyl.

(p) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkylsulfonyl
preferably aryl alkyl is aryl-C_{1-6} alkyl, more preferably aryl-C_{1-4} alkyl, in particular aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$CH(CH_2CH_3)$-, most preferably aryl-CH_2-. Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl. When the aryl moiety is substituted, it is preferably mono-, di- or tri-substituted. In one embodiment, phenyl is preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl,

-O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably substituted, phenyl or naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano. Suitable substituents for the phenyl and naphthyl substituent on the aryl moiety of aryl alkylcarbonyl include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino.

When R_b is acyl, R_c is as defined herein, preferably, R_c is hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl, unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, or preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or unsubstituted or substituted C_1-C_7-alkyl, most preferably cyclopropyl or methyl. In particular, when R_b is acyl as defined under (h) to (n), R_c is preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or unsubstituted or substituted C_1-C_7-alkyl, most preferably cyclopropyl or methyl. In particular, when R_b is acyl as defined under (o), R_c is preferably unsubstituted or substituted C_3-C_8-cycloalkyl most preferably cyclopropyl. In particular, when R_b is acyl as defined under (p), R_c is preferably unsubstituted or substituted C_3-C_8-cycloalkyl most preferably methyl or isobutyl.

When R_c is hydrogen, then one or more, preferably all of the following substituents have the following definition:
R_b is unsubstituted or substituted aryl as defined herein, preferably unsubstituted phenyl, unsubstituted or substituted aryl alkylcarbonyl as defined herein, preferably unsubstituted phenyl-$C(CH_3)_2$-CO or unsubstituted phenyl-CH(OMe)-CO, unsubstituted or substituted aryl carbonyl as defined herein, preferably unsubstituted indanyl-CO-, unsubstituted or substituted heterocyclyl carbonyl as defined herein, preferably unsubstituted 2,3-dihydro-benzo[1,4]dioxinyl-CO-, unsubstituted or substituted heterocyclyl alkyl carbonyl as defined herein, preferably unsubstituted tetrahydropyranyl-CH_2-CO-
R^1 is substituted phenyl carbonyl as defined herein, in particular whereby one substituent is –O-C_1-C_7-alkyl, such as OMe, or -C_1-C_7-alkyl, such as methyl or ethyl, and the other is -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, such as -OC_3H_6OMe;
R^2 is branched alkyl, such as isopropyl;
T is methylene, and
R^4 and R^5 are hydrogen.

When R_c is unsubstituted or substituted C_1-C_7-alkyl, preferred examples are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted. In a preferred embodiment, R_c is branched alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, and 1,2-dimethyl-propyl, most preferably isopropyl. In another preferred embodiment, R_c is straight chain alkyl such as methyl, ethyl, n-propyl, n-butyl or n-pentyl, more preferably methyl or ethyl, most preferably ethyl If the alkyl moiety is substituted, suitable substituents are as defined herein, preferably O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano. Most preferably, the alkyl moiety is unsubstituted.

When R_c is unsubstituted or substituted C_3-C_8-cycloalkyl, preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_3, C_4, C_5 and C_6-cycloalkyl, more preferably cyclopropyl or cyclobutyl, most preferably cyclopropyl. The cycloalkyl moiety may be substituted or unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, most preferably phenyl or naphthyl. Most preferably, the cycloalkyl moiety is unsubstituted.

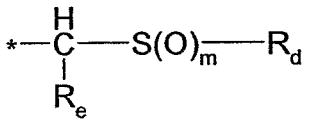
When R_c is unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, such as C_3-C_8-cycloalkyl-C_1-C_4-alkyl, in particular C_3-C_8-cycloalkyl-CH_2, preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_3, C_4, C_5 and C_6-cycloalkyl, most preferably cyclopropyl. The cycloalkyl moiety may be substituted or unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl,

carboxyl, and cyano, most preferably phenyl or naphthyl. Most preferably, the cycloalkyl moiety is unsubstituted.

When R_c is unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, then one or more, preferably all of the following substituents have the following definition:
R^1 is substituted phenyl carbonyl as defined herein, in particular whereby one substituent is -O-C_1-C_7-alkyl, such as OMe, or -C_1-C_7-alkyl, such as methyl or ethyl, and the other is -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, such as -OC_3H_6OMe;
R^2 is branched alkyl, such as isopropyl;
T is methylene, and
R^4 and R^5 are hydrogen.

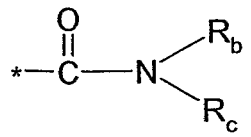
When R^3 is a moiety of formula (b), R_e is as defined herein, preferably, R_e is hydrogen.

R^3 is in a third embodiment a moiety of the formula (c)



In this embodiment, R_d is as defined herein, in particular R_d is unsubstituted or substituted phenyl- or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from those mentioned for unsubstituted of substituted phenyl- or naphthyl-C_1-C_7-alkyl under R_b , or is -$N(R_b)(R_c)$ wherein R_b and R_c are as defined for the second embodiment above, preferably is unsubstituted or [C_1-C_7-alkyl-, phenyl-, halo-lower alkyl-, halo, oxo-C_1-C_7-alkyl-, C_1-C_7-alkyloxy-, phenyl-C_1-C_7-alkoxy-, halo-C_1-C_7-alkyloxy-, phenoxy-, C_1-C_7-alkanoylamino-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted (phenyl- or naphthyl)-C_1-C_7-alkyl; most preferably benzyl.

R^3 is in a fourth embodiment a moiety of the formula (f)



In this embodiment, R_b is as defined herein, in particular as described with respect to the second embodiment where R^3 is a moiety of the formula (b). Preferably, R_b is aryl-alkyl, such as phenyl-C_1-C_4-alkyl, whereby the aryl moiety is unsubstituted or substituted by a suitable substituent such as C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano; preferably the aryl moiety is unsubstituted. Or R_b is unsubstituted or substituted alkyl. Preferred examples are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted, preferably straight chain alkyl such as methyl, ethyl, n-propyl, n-butyl or n-pentyl, preferably methyl, whereby the alkyl moiety is unsubstituted or substituted by a suitable substituent such as O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano; preferably the alkyl moiety is unsubstituted.

In this embodiment, R_c is as defined herein, preferably, R_c is hydrogen.

When R^3 is a moiety of the formula (f), then one or more, preferably all of the following substituents have the following definition:
R^1 is substituted phenyl carbonyl as defined herein, in particular whereby one substituent is –O-C_1-C_7-alkyl, such as OMe, or -C_1-C_7-alkyl, such as methyl or ethyl, and the other is -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, such as -OC_3H_6OMe;
R^2 is branched alkyl, such as isopropyl;
T is methylene, and
R^4 and R^5 are hydrogen.

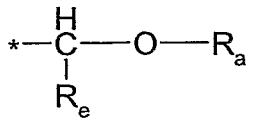
Particular embodiments of the invention, especially of compounds of the formula I and/or salts thereof, are provided in the Examples – the invention thus, in a very preferred embodiment, relates to a compound of the formula I, or a salt thereof, selected from the compounds given in the Examples, as well as the use thereof.

Process of Manufacture

A compound of formula I, or a salt thereof, is prepared analogously to methods that, for other compounds, are in principle known in the art, so that for the novel compounds of the formula I the process is novel at least as analogy process, especially as described or in ana-

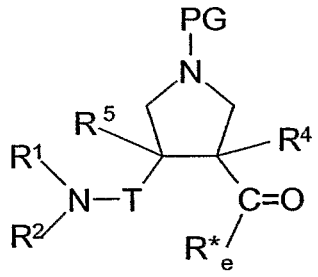
logy to methods described herein in the illustrative Examples, or modifications thereof, preferably in general by

(A) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (a)



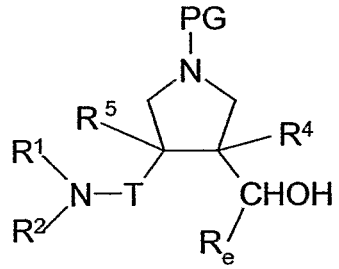
(a)

wherein R_a and R_e are as defined for a compound of the formula I and R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reducing a compound of the formula II,



(II)

wherein R^1, R^2, R^4, R^5 and T are as just defined, R^*_e is hydroxy or R_e as defined for a compound of the formula I and PG is a protecting group, to the corresponding hydroxy compound of the formula III,



(III)

wherein R_e is as defined for a compound of the formula I and the other moieties are as defined, which is then either deprotected to a corresponding compound of the formula I wherein R_a in the moiety of the formula (a) is hydrogen or further reacted either

(i) with a compound of the formula IV,

$$R_a^*\text{-}X \qquad \text{(IV)}$$

wherein R_a^* is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or acyl and X is a leaving group, or

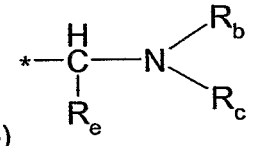
(ii) in order to introduce a moiety R_a which is N-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl or unsubstituted or substituted alkyl)-aminocarbonyl, with an isocyanato compound of the formula IV*,

$$R_a^{**}\text{-}N{=}C{=}O \qquad (IV^*)$$

wherein R_a^{**} is unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl or unsubstituted or substituted alkyl,

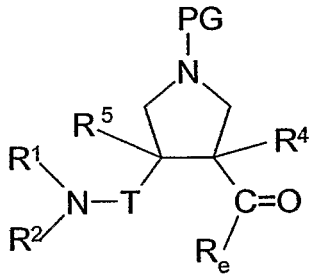
where reaction (i) or (ii) is followed by removal of any protecting group(s) to give a corresponding compound of the formula I if no further conversion requiring the presence of protecting groups is desired; or

(B) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (b)



(b)

wherein R_e, R_b and R_c are as defined for a compound of the formula I, and wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reacting an aldehyde compound of the formula V,



(V)

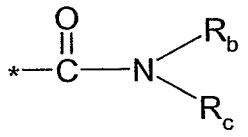
wherein R_e, R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group,

under conditions of reductive amination with a compound of the formula VI,

$$R_b\text{-}NH\text{-}R_c \qquad (VI)$$

wherein R_b and R_c are as defined for a compound of the formula I, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

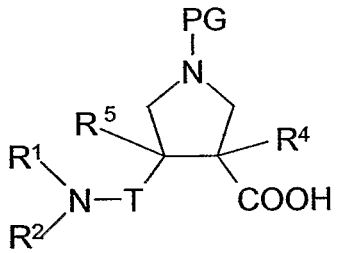
(C) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (f)



(f)

wherein R_b and R_c as well as R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I,

condensing an acid of the formula IIB,



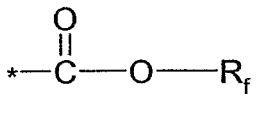
(IIB)

wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group, or a reactive derivative thereof, with an amine of the formula VI,

$$R_b\text{-NH-}R_c \qquad \text{(VI)}$$

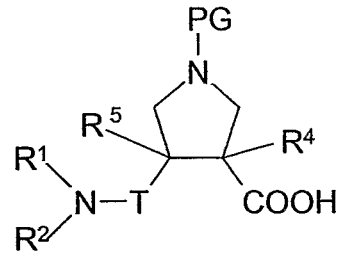
wherein R_b and R_c are as defined for a compound of the formula I, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

(D) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (g)



(g)

wherein R_f is as defined for a compound of the formula I and wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reacting an acid of the formula IIB,



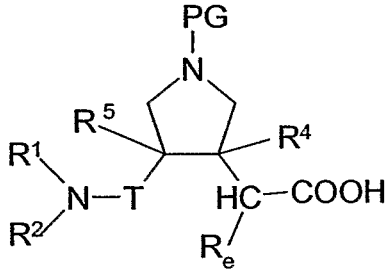
(IIB)

wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group, or a reactive derivative thereof, with an alcohol or alcohol derivative of the formula VII,

$$R_f\text{-}X \qquad \text{(VII)}$$

wherein R_f is as defined for a compound of the formula I and X is hydroxy or a leaving group, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

(E) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (d) or (e) as defined for a compound of the formula I and R^1, R^2, R' R^5 and T are as defined for a compound of the formula I, reacting a compound of the formula IIA,



(IIA)

wherein R^1, R^2, R^4, R^5, T and R_e are as defined for a compound of the formula I,

(i) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (d) with a compound of the formula VI,

$$R_b\text{-}NH\text{-}R_c \qquad \text{(VI)}$$

wherein R_a and R_b are as defined for a compound of the formula I, or

(ii) for the synthesis of a compound of the formula I wherein $R^3$is a moiety of the formula (e) with a compound of the formula VII,

$$R_f\text{-}X \qquad \text{(VII)};$$

wherein R_f is as defined for a compound of the formula I and X is hydroxy or a leaving group;

and, if desired, subsequent to any one or more of the processes (A), (B), (C),r (D) or (E) mentioned above, converting an obtainable compound of the formula I or a protected form thereof into a different compound of the formula I, converting a salt of an obtainable compound of formula I into the free compound or a different salt, converting an obtainable free compound of formula I into a salt thereof, and/or separating an obtainable mixture of isomers of a compound of formula I into individual isomers;

where in any of the starting materials (especially of the formulae II, IIA, IIB, III, IV, IV*, V, VI and VII), in addition to specific protecting groups mentioned, further protecting groups may be present, and any protecting groups are removed at an appropriate stage in order to obtain a corresponding compound of the formula I, or a salt thereof.

Preferred Reaction Conditions

The preferred reaction conditions for the reactions mentioned above, as well as for the transformations and conversions, are as follows (or analogous to methods used in the Examples or as described there):

The reduction under (A) preferably takes place under customary conditions for the reduction of carbonic acids to the corresponding alcohols, preferably in the presence of an appropriate complex hydride, such as borane-dimethylsulfide-complex, in an appropriate solvent, e.g. an ether, such as tetrahydrofurane, at preferred temperatures e.g. from –40 to 30 °C, e.g. from – 15 to 0 °C, or e.g. with disiamylborane or $LiAlH[OC(CH_3]_3$ in tetrahydrofurane or diethylether, sodium borohydride in ethanol or sodium borohydride in the presence of LiCl in diglycol, or the like, at preferred temperatures in the range from 0 °C to the reflux temperature of the reaction mixture.

The subsequent removal of a protecting group, e.g. PG, such as tert-butoxycarbonyl, methoxymethyl, benzyl, 2-(trimethylsilyl)-ethoxycarbonyl or tert-butyldimethylsilyl, if required, takes place under standard conditions, see also the literature mentioned below under General Process Conditions. For example, tert-butoxycarbonyl is removed in the presence of an acid, e.g. a hydrohalic acid, such as HCl, in an appropriate solvent, e.g. an ether, such as dioxane, or an alcohol, e.g. isopropanol, at customary temperatures, e.g. at room temperature, the removal of benzyl by treatment with hydrogen in the presence of a noble metal catalyst, such as palladium on charcoal, under customary reaction conditions, e.g. in an appropriate solvent, such as methanol or ethanol, and at customary temperatures, e.g. from 0 to 50 °C, the removal of 2-(trimethylsilyl)-ethoxycarbonyl can be achieved, for example, by reaction with a tetra-lower alkylammonium fluoride, such as tetraethylammoniumfluoride, in an appropriate solvent or solvent mixture, e.g. a halogenated hydrocarbon, such as methylene chloride, and/or a nitrile, such as acetonitrile, preferably at elevated temperatures, e.g. under reflux conditions, and the removal of tert-butyldimethylsilyl

in the presence of tetra-butyl ammonium fluoride, e.g. in the presence of a solvent such as tetrahydrofurane at preferred temperatures from 0 to 50 °C, e.g. at about room temperature.

The further reaction under (A) (i) (preferably with a still protected compound of the formula III) with a compound of the formula IV then preferably takes place under customary conditions for substitution reaction, e.g. in an appropriate solvent, such as an ether, e.g. tetrahydrofurane, or a halogenated hydrocarbon, e.g. methylene chloride, at appropriate temperatures, e.g. in the range from –40 °C to the reflux temperature, if useful or required in the presence of a base, such as potassium carbonate. The leaving group X is preferably halo, especially chloro, bromo or iodo, alkanesulfonyloxy, such as methanesulfonyloxy, or arylsulfonyloxy, such as p-toluolsulfonyloxy.

The further reaction under (A) (ii) (preferably with a still protected compound of the formula III) with a compound of the formula IV*, alternatively, then preferably takes place under customary conditions for the reaction of hydroxy compounds with isocyanates, for example, the reaction preferably takes place in the presence of a Lewis Acid, such as aluminium chloride, in an appropriate solvent, such as diethylether, at preferred temperatures e.g. from 0 to 50 °C. Where required, subsequent removal of protecting groups takes place as described above or below, especially as described under the general process conditions.

The reductive amination under (B) preferably takes place place under customary conditions for reductive amination, e.g. in the presence of an appropriate reducing (e.g. hydrogenation) agent, such as hydrogen in the presence of a catalyst or a complex hydride, e.g. sodium triacetoxyborohydride or sodium cyanoborohydride, in an appropriate solvent, such as a halogenated hydrocarbon, e.g. methylene chloride or 1,2,-dichloroethane, and optionally a carbonic acid, e.g. acetic acid, at preferred temperatures between -10 °C and 50 °C, e.g. from 0 °C to room temperature; if required, the subsequent removal of protecting groups takes place e.g. as described above under (A).

The condensation of an acid of the formula II, or a reactive derivative thereof, under (C) preferably takes place under customary condensation conditions, where among the possible reactive derivatives of an acid of the formula II reactive esters (such as the hydroxybenzotriazole (HOBT), pentafluorophenyl, 4-nitrophenyl or N-hydroxysuccinimide ester), acid halogenides (such as the acid chloride or bromide) or reactive anhydrides (such

as mixed anhydrides with lower alkanoic acids or symmetric anhydrides) are preferred. Reactive carbonic acid derivatives can also and preferably be formed in situ. The reaction is carried out by dissolving the compounds of formulae II and VI in a suitable solvent, for example a halogenated hydrocarbon, such as methylene chloride, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methyl-2-pyrrolidone, methylene chloride, or a mixture of two or more such solvents, and by the addition of a suitable base, for example triethylamine, diisopropylethylamine (DIEA) or *N*-methylmorpholine and, if the reactive derivative of the acid of the formula II is formed *in situ*, a suitable coupling agent that forms a preferred reactive derivative of the carbonic acid of formula III *in situ*, for example dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/ HOBT); bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl); *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TPTU); O-benzotriazol-1-yl)-N,N,N', N'-tetramethyluronium tetrafluoroborate (TBTU); (benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate (PyBOP), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride/hydroxybenzotriazole or/1-hydroxy-7-azabenzotriazole (EDC/HOBT or EDC/HOAt) or HOAt alone, or with (1-chloro-2-methyl-propenyl)-dimethylamine. For review of some other possible coupling agents, see e.g. Klauser; Bodansky, *Synthesis* **1972**, 453-463. The reaction mixture is preferably stirred at a temperature of between approximately -20 and 50 °C, especially between 0 °C and 30 °C, e.g. at room temperature. The reaction may preferably carried out under an inert gas, e.g. nitrogen or argon. If required, the subsequent removal of protecting groups takes place e.g. as described above under (A).

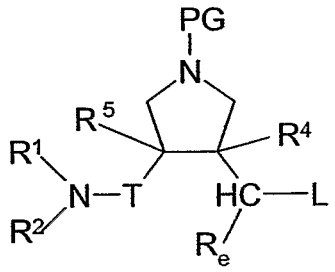
The esterification under (D) can be carried out under comparable reaction conditions as described for the condensation under (C) described in the preceding paragraph, and also the reactive derivatives of the acid of the formula II may be as described there, if in the compound of the formula VII X is hydroxy. Where X is a leaving group, especially halogen, the reaction takes place in the presence of a base. If required, the subsequent removal of protecting groups takes place e.g. as described above under (A).

The condensation under reaction (E) (i) preferably takes place under conditions as mentioned above for reaction (C), the esterification under reaction (E) (ii) with compounds of the formula VII wherein X is OH preferably takes place under conditions mentioned above for reaction (D), the reaction (e) (ii) with compounds of the formula VII wherein X is a leaving group, preferably halogen, can take place in the presence of a base.

Optional Reactions and Conversions

Compounds of the formula I, or protected forms thereof directly obtained according to any one of the preceding procedures (meaning that, if conversion is desired, a removal of protecting groups is not required under (A), (B), (C), (D) or (E) or after introducing protecting groups anew, which are included subsequently as starting materials for conversions as well even if not mentioned specifically, can be converted into different compounds of the formula I according to known procedures, where required after removal of protecting groups.

For example, a compound of the formula I wherein R_1, R_2, R_4, R_5 and T are as defined for compounds of the formula I above or below and wherein R^3 is a group of the formula (a) mentioned above wherein R_e is as defined for a compound of the formula I and R_a is hydrogen (which compound may be used in free or preferably in protected form, e.g. a compound of the formula III given above) may be converted into the corresponding compound of the formula VIII,

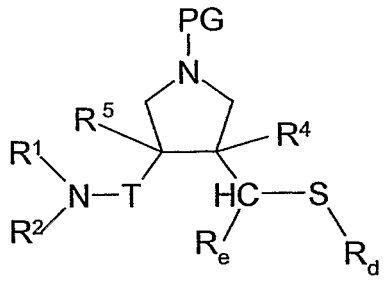


(VIII)

wherein R_e, R_1, R_2, R_4, R_5 and T are as just defined, PG is a protecting group and L is a leaving group, especially a C_1-C_7-alkanesulfonyloxy, such as methanesulfonyloxy, or arylsulfonyloxy, such as toluenesulfonyloxy, preferably by reaction with the corresponding alkane- or arylsulfonylhalogenide, e.g. –chloride, under customary conditions, e.g. in the absence or presence of an appropriate solvent, such as an ether or a halogenated hydrocarbon, in the presence of a tertiary nitrogen base, such as triethylamine, at temperatures e.g. from –20 °C to the reflux temperature of the reaction mixture, giving a corresponding compound of the formula VIII; the latter can then be deprotected to give the corresponding compound of the formula I, or reacted with a mercapto compound of the formula X,

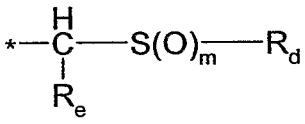
$$R_d\text{-SH} \qquad (X)$$

wherein R_d is a moiety as defined as for a compound of the formula I other than of the formula $-N(R_a)(R_b)$, to give a corresponding compound of the formula XI,



(XI)

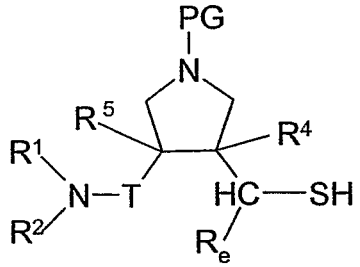
wherein R_1, R_2, R_4, R_5 and T are as just defined and PG is a protecting group, which may then be deprotected to give a compound of the formula I wherein R^3 is a moiety of the formula (c)



(c)

wherein R_e is as defined for a compound of the formula I, m is 0 (zero) and R_d is as defined for a compound of the formula X; or converted by oxidation, e.g. with an organic peroxide, such as m-chloro-perbenzoic acid, in an appropriate solvent, e.g. dimethylformamide, tetrahydrofurane or methylene chloride, to the corresponding compound wherein m is 2 which after deprotection gives the corresponding compound of the formula I.

Alternatively, a compound of the formula I wherein R_1, R_2, R_4, R_5 and T are as defined for compounds of the formula I above or below and wherein R^3 is a group of the formula (a) mentioned above wherein R_e is as defined for a compound of the formula I and R_a is hydrogen (which compound may be used in free or preferably in protected form, e.g. a compound of the formula III given above) may be converted into a compound of the formula VIII as described above which is then reacted with a C_1-C_7-alkanoyl-thiolate, e.g. an alkalimetal (such as sodium) thiolate, to the corresponding compound of the formula XI given above wherein R_d is C_1-C_7-alkanoyl, such as acetyl, which is then hydrolyzed, e.g. with lithium hydroxide, under customary conditions to the corresponding free mercapto compound of the formula XIA,



(XIA)

which is then either

(i) reacted with a compound of the formula XA,

R_d-Hal (XA)

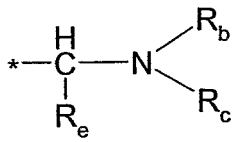
wherein Hal is halo and R_d has a meaning as defined herein other than -N($R_b$$R_c$), to a corresponding protected version of a compound of the formula I which can then be deprotected to give the corresponding compound of the formula I wherein R_d is as defined for a compound of the formula XA, or which can first be oxidised to a protected version of a compound of the formula I wherein m is 1 or preferably 2, for example with a peroxide, such as m-chloro-perbenzoic acid, and then deprotected to give the corresponding compound of the formula I; or

(ii) oxidized with a peroxide, such as hydrogen peroxide, and subsequently reacted with a halogenating agent, such as phosphorous oxychloride or oxalyl chloride, to the corresponding compound wherein instead of the SH group an $S(O)_2$-Hal group, e.g. wherein Hal is halo, especially chloro, is present, which can then be reacted with a compound of the formula VI

R_b-NH-R_c (VI)

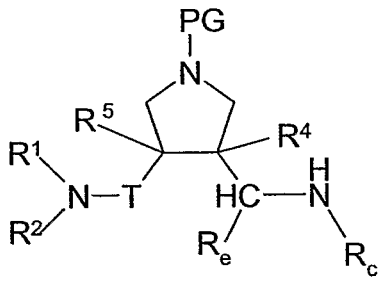
as defined above to give, after deprotection, a corresponding compound of the formula I wherein R_d is a group of the formula –N(R_b)(R_c).

In a compound of the formula I wherein R^3 is a moiety of the formula (b)



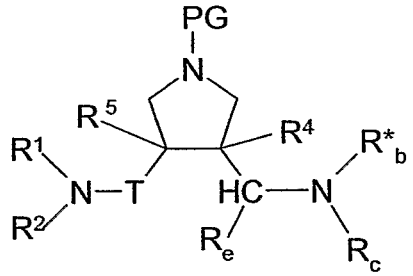
(b)

wherein R_e is as defined for a compound of the formula I, R_c is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl and R_b is hydrogen, or preferably a protected derivative thereof, e.g. of the formula XII,



(XII)

wherein PG is a protecting group and the other moieties are as defined for a compound of the formula I, can be converted into the acylated compound of the formula XIII,



(XIII)

wherein R^*_b is acyl and the other moieties are as defined for a compound of the formula XII, by reaction with a corresponding acid of the formula XIV,

$$R^*_b\text{-OH} \qquad \text{(XIV)}$$

wherein R^*_b is acyl, or a reactive derivative thereof. Removal of the protecting group(s) then leads to the corresponding compound of the formula I wherein R^3 is a moiety of the formula (b) as just given wherein R_e and R_c are as defined for a compound of the formula XII and R_b is acyl.

An oxo group in a compound of the formula I, e.g. carbonyl as T, may be converted to the corresponding thioxo, e.g. thiocarbonyl, group by reaction with Lawesson`s reagent under customary reaction conditions.

Salts of compounds of formula I having at least one salt-forming group may be prepared in a manner known *per se*. For example, salts of compounds of formula I having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, e.g. the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming

agent preferably being used. Acid addition salts of compounds of formula I are obtained in customary manner, e.g. by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of formula I containing acid and basic salt-forming groups, e.g. a free carboxy group and a free amino group, may be formed, e.g. by the neutralisation of salts, such as acid addition salts, to the isoelectric point, e.g. with weak bases, or by treatment with ion exchangers.

A salt of a compound of the formula I can be converted in customary manner into the free compound; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent. In both cases, suitable ion exchangers may be used.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known per se by means of appropriate separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of one of the starting compounds or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

Intermediates and final products can be worked up and/or purified according to standard methods, e.g. using chromatographic methods, distribution methods, (re-) crystallization, and the like. Some possible methods that can also be used with other compounds analogously can be found in the Examples.

Starting Materials

In the subsequent description of starting materials (which term also includes intermediates) and their synthesis, R^1, R^2, R^3, R^4, R^5, T, m, R_a, R_b, R_c, R_d, R_e, R_f and PG have the meanings given above or in the Examples for the respective starting materials or intermediates, if not indicated otherwise directly or by the context. Protecting groups, if not specifically mentioned, can be introduced and removed at appropriate steps in order to prevent functional groups, the reaction of which is not desired in the corresponding reaction step or steps, from participating in a reaction, employing protecting groups, methods for their

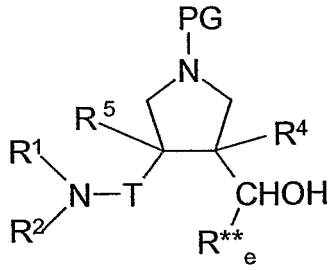
introduction and their removal are as described above or below, e.g. in the references mentioned under "General Process Conditions". The person skilled in the art will readily be able to decide whether and which protecting groups are useful or required and at which stage it is appropriate to introduce , exchange and/or remove protecting groups.

A compound of the formula II wherein R^*_e is hydrogen (which is a compound of the formula V wherein R^*_e is hydrogen) can be obtained from a compound of the formula IIB or of the formula XV given below by reduction of the (in the case of formula XV esterified, e.g. by C_1-C_7-alkyloxy) carboxy function, e.g. with an appropriate complex hydride, such as borane-dimethylsulfide complex, in an appropriate solvent, such as an ether, e.g. tetrahydrofurane, at preferred temperatures between –50 °C and the reflux temperature of the reaction mixture, e.g. at –30 to 60 °C.

A compound of the formula II wherein R^*_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (especially) substituted or preferably unsubstituted C_1-C_7-alkyl (which is a compound of the formula V wherein R_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (especially) substituted or preferably unsubstituted C_1-C_7-alkyl) can, for example, be obtained from a compound of the formula V wherein R^*_e is hydrogen by reaction with a grignard reagent of the formula XXII,

$$R^{**}_e\text{-Mg-Hal} \qquad \text{(XXII)}$$

wherein R^{**}_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (especially) substituted or preferably unsubstituted C_1-C_7-alkyl and Hal is halo, especially chloro or bromo, under customary reaction conditions, e.g. in an ether, such as diethylether, at preferred temperatures from 0 °C to the reflux temperature of the reaction mixture, to give a compound of the formula IIIA,

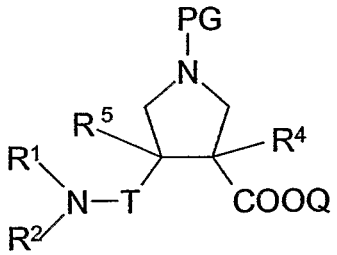


(IIIA)

wherein R^{**}_e is as just described (which is a compound of the formula III wherein R^*_e is as just defined for R^{**}_e); which is then oxidized, e.g. in the presence of an appropriate oxidant, such as Dess-Martin-periodinane, in an appropriate solvent, e.g. a halogenated hydrocarbon, e.g. methylene chloride, at preferred temperatures from 0 °C to 50 °C, e.g. at room temperature, to give the corresponding compound of the formula II or V.

Alternatively, a compound of the formula II wherein R^*_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (especially) substituted or preferably unsubstituted C_1-C_7-alkyl can be reacted in the presence of a condensation agent, e.g. under reaction conditions and with reagents as described under process variants (C) and (D) above, with N,O-dimethyl hydroxylamine to form the corresponding Weinreb amide which can then directly be reacted with a Grignard reagent of the formula XXII as described above to a corresponding compound of the formula II or V.

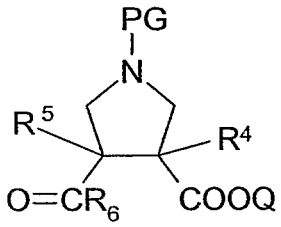
A compound of the formula IIB (which is a compound of the formula II wherein R^*_e is hydroxy) can be prepared from a corresponding ester of the formula XV,



(XV)

wherein Q is an organic moiety, preferably substituted or especially unsubstituted C_1-C_7-alkyl, by hydrolysis in the presence of a base, e.g. an alkaline metal hydroxide, such as lithium hydroxide, in an appropriate solvent, e.g. a hydroxy lower alkane, such as methanol, in the presence of water and preferably at temperatures e.g. from 0 to 50 °C.

A compound of the formula XV wherein T is methylene or methylene mono-substituted by alkyl (-[C(H)(alkyl)]-) can, for example, be obtained by reacting an aldehyde or keto compound of the formula XVI,



(XVI)

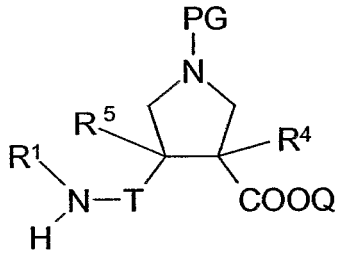
wherein Q is as described for a compound of the formula XV and R_6 is alkyl or preferably hydrogen with an amine of the formula XVII,

$$R^1\text{-NH-}R^2 \qquad \text{(XVII)}$$

under conditions of reductive amination, e.g. under the reaction conditions described for reaction (B) above. If instead of a compound of the formula XVII a compound of the formula XVII*,

$$H_2\text{-N-}R_1 \qquad \text{(XVII*)}$$

is used, a compound of the formula XV* results,



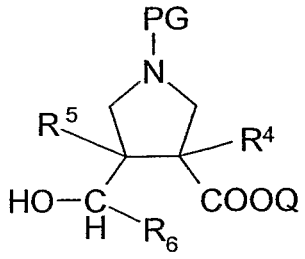
(XV*)

wherein Q is as defined for a compound of the formula XV, which can then be converted into a compound of the formula XV by reaction with a compound of the formula XVIII,

$$R_2\text{-Y} \qquad \text{(XVIII)}$$

wherein Y, if R_2 is acyl, is either hydroxy or the compound is a reactive derivative, e.g. wherein Y is halo or an activating group formed in situ, preferably under conditions analogous to those in reaction (C) above; or Y, if R_2 is one of the moieties defined for R_2 in compounds of the formula I other than acyl, is a leaving group, e.g. as defined for X in a compound of the formula IV above and under reaction conditions analogous to those described above for the reaction under (A) (i).

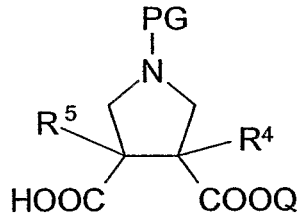
A compound of the formula XVI wherein R_6 is alkyl or preferably hydrogen can, for example, be obtained from a hydroxy compound of the formula XIX,



(XIX)

wherein R_6 is alkyl or preferably hydrogen and Q is as defined for a compound of the formula XV by oxidation to the corresponding oxo compound of the formula XVI which preferably takes place in the presence of an appropriate oxidant, such as Dess-Martin-periodinane, in an appropriate solvent, e.g. a halogenated hydrocarbon, e.g. methylene chloride, at preferred temperatures from 0 °C to 50 °C, e.g. at room temperature.

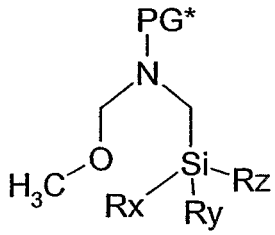
A hydroxy compound of the formula XIX wherein R_6 is hydrogen can, for example, be obtained from a compound of the formula XX,



(XX)

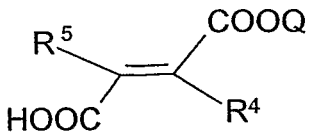
wherein Q is as defined for a compound of the formula XV by reduction in the presence of an appropriate complex hydride, e.g. borane dimethylsulfide complex, in an appropriate solvent, such as an ether, e.g. tetrahydrofurane, at preferred temperatures between –50 ° and the reflux temperature of the reaction mixture, e.g. at –30 to 60 °C.

A compound of the formula XX may, inter alia, be obtained by reacting a compound of the formula XXI,



(XXI)

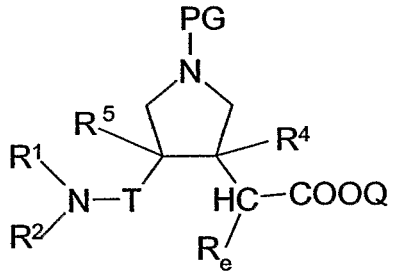
wherein PG* is a protecting group that withstands the reaction, e.g. benzyl, and each of Rx, Ry and Rz are alkyl, preferably C1-C7-alkyl, especially methyl, with a fumaric acid derivative of the formula XXII,



(XXI)

wherein each of R^4 and R^5 preferably has one of the meanings given for R^4 and R^5 other than hydroxy, more preferably is C_1-C_7-alkyl, e.g. methyl or ethyl, or is hydrogen, in the presence of an acid, e.g. trifluoroacetic acid, in an appropriate solvent, such as y halogenated hydrocarbon, e.g. methylene chloride, at preferred temperatures e.g. in the range from –30 to 50 °C, yielding the corresponding compound of the formula XX wherein preferably the protecting group PG* can be replaced with a different protecting group PG useful for subsequent reactions, such as tert-butoxycarbonyl, for example benzyl PG* can be removed with hydrogen in the presence of a hydrogenation catalyst, especially a noble metal catalyst, preferably on a carrier material, such as charcoal, e.g. Pd/C, in an appropriate solvent, such as an alcohol, e.g. ethanol, at temperatures e.g. from –10 to 60 °C, and tert-butoxycarbonyl may be introduced in the same step or subsequently by reaction with tert-butoxycarbonic anhydride.

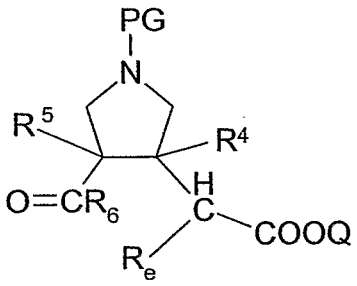
A compound of the formula IIA can, for example, be prepared from a corresponding ester of the formula XVA,



(XVA)

wherein Q is an organic moiety, preferably substituted or especially unsubstituted C_1-C_7-alkyl, by hydrolysis in the presence of a base, e.g. an alkaline metal hydroxide, such as lithium hydroxide, in an appropriate solvent, e.g. a hydroxy lower alkane, such as methanol, in the presence of water and preferably at temperatures e.g. from 0 to 50 °C.

A compound of the formula XVA wherein T is methylene or methylene mono-substituted by alkyl (-[C(H)(alkyl)]-) can, for example, be obtained by reacting an aldehyde or keto compound of the formula XVIA,



(XVIA)

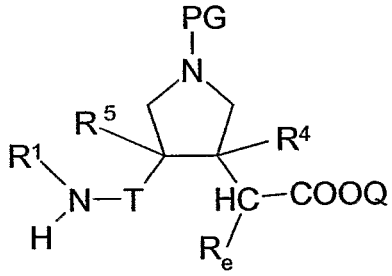
wherein Q is as described for a compound of the formula XVA and R_6 is alkyl or preferably hydrogen with an amine of the formula XVII,

$$R^1\text{-NH-}R^2 \qquad \text{(XVII)}$$

under conditions of reductive amination, e.g. under the reaction conditions described for reaction (B) above. If instead of a compound of the formula XVII a compound of the formula XVII*,

$$H_2\text{-N-}R_1 \qquad \text{(XVII*)}$$

is used, a compound of the formula XVA* results,



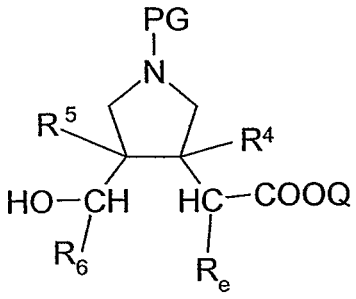
(XVA*)

wherein Q is as defined for a compound of the formula XVA, which can then be converted into a compound of the formula XVA by reaction with a compound of the formula XVIII,

$$R_2\text{-Y} \qquad \text{(XVIII)}$$

wherein Y, if R_2 is acyl, is either hydroxy or the compound is a reactive derivative, e.g. wherein Y is halo or an activating group formed in situ, preferably under conditions analogous to those in reaction (C) above; or Y, if R_2 is one of the moieties defined for R_2 in compounds of the formula I other than acyl, is a leaving group, e.g. as defined for X in a compound of the formula IV above and under reaction conditions analogous to those described above for the reaction under (A) (i).

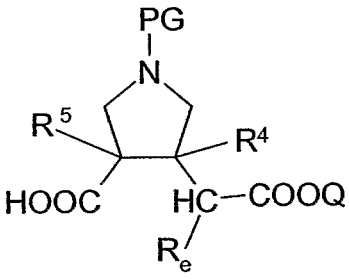
A compound of the formula XVIA wherein R_6 is alkyl or preferably hydrogen can, for example, be obtained from a hydroxy compound of the formula XIXA,



(XIXA)

wherein R_6 is alkyl or preferably hydrogen and Q is as defined for a compound of the formula XVA by oxidation to the corresponding oxo compound of the formula XVIA which preferably takes place in the presence of an appropriate oxidant, such as Dess-Martin-periodinane, in an appropriate solvent, e.g. a halogenated hydrocarbon, e.g. methylene chloride, at preferred temperatures from 0 °C to 50 °C, e.g. at room temperature.

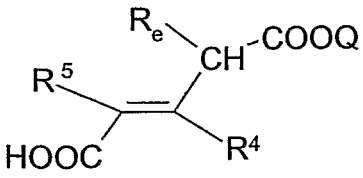
A hydroxy compound of the formula XIXA wherein R_6 is hydrogen can, for example, be obtained from a compound of the formula XXA,



(XXA)

wherein Q is as defined for a compound of the formula XV by reduction in the presence of an appropriate complex hydride, e.g. borane dimethylsulfide complex, in an appropriate solvent, such as an ether, e.g. tetrahydrofurane, at preferred temperatures between –50 ° and the reflux temperature of the reaction mixture, e.g. at –30 to 60 °C.

A compound of the formula XXA may, inter alia, be obtained by reacting a compound of the formula XXI, as described above, with a fumaric acid derivative of the formula XXIA,



(XXIA)wherein each of R^4 and R^5 preferably has one of the meanings given for R^4 and R^5 other than hydroxy, more preferably is C_1-C_7-alkyl, e.g. methyl or ethyl, or is hydrogen, in the presence of an acid, e.g. trifluoroacetic acid, in an appropriate solvent,

such as y halogenated hydrocarbon, e.g. methylene chloride, at preferred temperatures e.g. in the range from –30 to 50 °C, yielding the corresponding compound of the formula XXA wherein preferably the protecting group PG* can be replaced with a different protecting group PG useful for subsequent reactions, such as tert-butoxycarbonyl, for example benzyl PG* can be removed with hydrogen in the presence of a hydrogenation catalyst, especially a noble metal catalyst, preferably on a carrier material, such as charcoal, e.g. Pd/C, in an appropriate solvent, such as an alcohol, e.g. ethanol, at temperatures e.g. from –10 to 60 °C, and tert-butoxycarbonyl may be introduced in the same step or subsequently by reaction with tert-butoxycarbonic anhydride.

A compound of the formula IIA may also be obtained by reacting a compound of the formula VIII as described above with a cyanide salt, e.g. an alkali metal cyanide, such as sodium or potassium cyanide, to the corresponding compound wherein instead of the –C(H)(R_e)-L group a –C(H)(R_e)-CN group is present, followed by hydrolysis with a base, such as sodium hydroxide, or under mild conditions by reaction first with H_2S resulting in a corresponding thioamide which can then be hydrolysed under mild conditions to give a corresponding compound of the formula IIA.

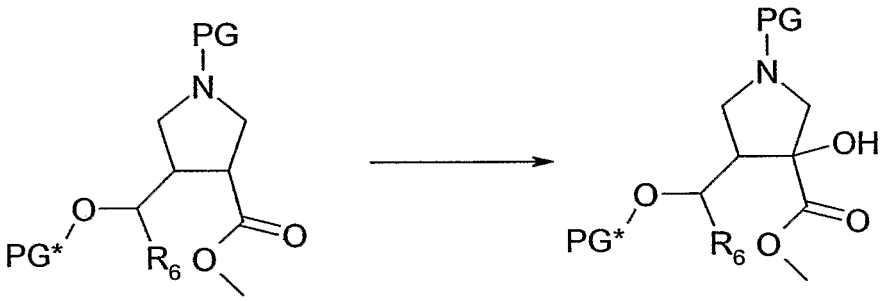
A compound of the formula XV or XVA wherein T is carbonyl (and Q is as defined for compounds of the formula XV above) can, for example, be obtained by reacting a compound of the formula XX or XXA, respectively, as defined above, or a reactive derivative thereof, under conditions analogous to those described above for the condensation reaction under process variant (C) with a compound of the formula XVII as defined above.

In the preceding starting materials (and final products), R^4 and R^5 are preferably hydrogen, with less preference unsubstituted or substituted alkyl, esterified or etherified hydroxy, with still less preference (in the intermediates preferably protected) hydroxy.

Hydroxy R^4 and/or R^5 can be introduced into starting materials at various stages, e.g. in (preferably appropriately protected) compounds of the formula XV,
for example by treatment with a strong base to remove the hydrogen to be substituted by R^4 or R^5, such as lithium hexamethyldisialazide (LHMDS) or preferably lithium diisopropylamide in tetrahydrofuran at low temperatures, e.g. from –100 to –50 °C, such as at –78 °C,

followed by oxidation e.g. by addition of an oxaziridine derivative according to Davis (e.g. 2-tert-butoxycarbonyl-3-trichloromethyl-oxaziridine or 2-(phenylsulfonyl or tolylsulfonyl)-3-phenyl-oxaziridine or (e.g. for stereoselective synthesis) (+)- or (-)-(camphorsulfonyl)oxaziridine) to give the corresponding hydroxy compound.

An alternative is the transformation on the following O-protected alcohol shown on the left (a compound of the formula XIX) to give an intermediate (shown on the right, also a compound of the formula XIX) that can be used either to build a final pyrrolidine where R^5 or R^4 are OH or etherified or esterified hydroxy depending on the sequence of reactions used:



wherein in both formulae PG* is a hydroxy protecting group, under comparable reacrtion conditions as just mentioned or other customary conditions.

Hydroxy R^4 and/or R^5 may then further be esterified or etherified according to standard procedures to give the corresponding compounds wherein $R^4$and/or R^5 is esterified or etherified hydroxy.
Other starting materials, such as also the starting materials of the formula IV, IV*, VI, VII, X and XIV are known in the art, can be prepared according to methods that are known in the art and/or are commercially available.

General Process Conditions

The following applies in general to all processes mentioned hereinbefore and hereinafter, while reaction conditions specifically mentioned above or below are preferred:

In any of the reactions mentioned hereinbefore and hereinafter, protecting groups may be used where appropriate or desired, even if this is not mentioned specifically, to protect functional groups that are not intended to take part in a given reaction, and they can be introduced and/or removed at appropriate or desired stages. Reactions comprising the use

of protecting groups are therefore included as possible wherever reactions without specific mentioning of protection and/or deprotection are described in this specification.

Within the scope of this disclosure only a readily removable group that is not a constituent of the particular desired end product of formula I is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and the reactions appropriate for their introduction and removal are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of Organic Chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (*Amino acids, Peptides, Proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of Carbohydrates: Monosaccharides and Derivatives*), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e. without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (e.g. by enzymatic cleavage).

All the above-mentioned process steps can be carried out under reaction conditions that are known per se, preferably those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, preferably solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, e.g. in the H^+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190°C, preferably from approximately -80°C to approximately 150°C, for example at from -80 to -60°C, at room temperature, at from -20 to 40 °C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower

alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofurane or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, e.g. as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or N-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of these, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The invention relates also to those forms of the processes in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ. In the processes of the present invention those starting materials are preferably used which result in compounds of formula I described as being preferred. Special preference is given to reaction conditions that are identical or analogous to those mentioned in the Examples. The invention relates also to novel starting compounds and intermediates described herein, especially those leading to novel compounds of the formula I or compounds of the formula I mentioned as preferred herein.

Pharmaceutical use, pharmaceutical preparations and methods

As described above, the compounds of the present invention are inhibitors of renin activity and, thus, may be of use for the treatment of hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth and/or hyperaldosteronism, and/or further cognitive impairment, alzheimers, dementia, anxiety states and cognitive

disorders, and the like. Hypertension, at least as one component of the disease to be treated, is especially preferred, meaning that hypertension alone or in combination with one or more (especially of the mentioned) other diseases may be treated (prophylactically and/or therapeutically).

The present invention further provides pharmaceutical compositions comprising a therapeutically effective amount of a pharmacologically active compound of the instant invention, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmaceutical compositions according to the present invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, to inhibit renin activity, and for the treatment of conditions associated with (especially inappropriate) renin activity. Such conditions include hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth and/or hyperaldosteronism, and/or further cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders and the like. Especially preferred is a disease which comprises hypertension, more especially hypertension itself, where treatment with a pharmaceutical composition or the use of a compound of the formula I for its synthesis is useful prophylactically and/or (preferably) therapeutically.

Thus, the pharmacologically active compounds of the invention may be employed in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with:

a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired

d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or
e) absorbants, colorants, flavors and sweeteners.

Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions.

Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, preferably about 1-50%, of the active ingredient.

Suitable formulations for transdermal application include a therapeutically effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and pre-determined rate over a prolonged period of time, and means to secure the device to the skin.

Accordingly, the present invention provides pharmaceutical compositions as described above for the treatment of conditions mediated by renin activity, preferably, hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth and/or hyperaldosteronism, and/or further cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders, as well as methods of their use.

The pharmaceutical compositions may contain a therapeutically effective amount of a compound of the formula I as defined herein, either alone or in a combination with another therapeutic agent, e.g., each at an effective therapeutic dose as reported in the art. Such therapeutic agents include:

a) antidiabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; peroxisome proliferator-activated receptor (PPAR) ligands; protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose cotransporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; and DPPIV (dipeptidyl peptidase IV) inhibitors such as LAF237;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) anti-obesity agents such as orlistat; and

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors.

Other specific anti-diabetic compounds are described by Patel Mona in *Expert Opin Investig Drugs*, 2003, 12(4), 623-633, in the figures 1 to 7, which are herein incorporated by reference. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The structure of the therapeutic agents identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

Accordingly, the present invention provides pharmaceutical products or compositions comprising a therapeutically effective amount of a compound of the invention alone or in combination with a therapeutically effective amount of another therapeutic agent, preferably selected from anti-diabetics, hypolipidemic agents, anti-obesity agents or anti-hypertensive agents, most preferably from antidiabetics, anti-hypertensive agents or hypolipidemic agents as described above.

The present invention further relates to pharmaceutical compositions as described above for use as a medicament.

The present invention further relates to use of pharmaceutical compositions or combinations as described above for the preparation of a medicament for the treatment of conditions mediated by (especially inappropriate) renin activity, preferably, hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth and/or hyperaldosteronism, and/or further cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders, and the like.

Thus, the present invention also relates to a compound of formula I for use as a medicament, to the use of a compound of formula I for the preparation of a pharmaceutical composition for the prevention and/or treatment of conditions mediated by (especially inappropriate) renin activity, and to a pharmaceutical composition for use in conditions mediated by (especially inappropriate) renin activity comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier material therefore.

The present invention further provides a method for the prevention and/or treatment of conditions mediated by (especially inappropriate) renin activity, which comprises administering

a therapeutically effective amount of a compound of the present invention to a warm-blooded animal, especially a human, in need of such treatment.

A unit dosage for a mammal of about 50-70 kg may contain between about 1 mg and 1000 mg, advantageously between about 5-600 mg of the active ingredient. The therapeutically effective dosage of active compound is dependent on the species of warm-blooded animal (especially mammal, more especially human), the body weight, age and individual condition, on the form of administration, and on the compound involved.

In accordance with the foregoing the present invention also provides a pharmaceutical product comprising a therapeutic combination, e.g., a kit, kit of parts, e.g., for use in any method as defined herein, comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, to be used concomitantly or in sequence with at least one pharmaceutical composition comprising at least another therapeutic agent, preferably selected from anti-diabetic agents, hypolipidemic agents, anti-obesity agents or anti-hypertensive agents. The kit may comprise instructions for its administration.

Similarly, the present invention provides a kit of parts comprising: (i) a pharmaceutical composition comprising a compound of the formula I according to the invention; and (ii) a pharmaceutical composition comprising a compound selected from an anti-diabetic, a hypolipidemic agent, an anti-obesity agent, an anti-hypertensive agent, or a pharmaceutically acceptable salt thereof, in the form of two separate units of the components (i) to (ii).

Likewise, the present invention provides a method as defined above comprising co-administration, e.g., concomitantly or in sequence, of a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and at least a second drug substance, said second drug substance preferably being an anti-diabetic, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent, e.g., as indicated above.

Preferably, a compound of the invention is administered to a mammal in need thereof.

Preferably, a compound of the invention is used for the treatment of a disease which responds to a modulation of (especially inappropriate) renin activity.

Preferably, the condition associated with (especially inappropriate) renin activity is selected from hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary

syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth and/or hyperaldosteronism, and/or further cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders.

Finally, the present invention provides a method or use which comprises administering a compound of formula I in combination with a therapeutically effective amount of an anti-diabetic agent, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent.

Ultimately, the present invention provides a method or use which comprises administering a compound of formula I in the form of a pharmaceutical composition as described herein.

The above-cited properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, rabbits, dogs, monkeys or isolated organs, tissues and preparations thereof. Said compounds can be applied *in vitro* in the form of solutions, e.g., preferably aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, e.g., as a suspension or in aqueous solution. The concentration level *in vitro* may range between about 10^{-3} molar and 10^{-10} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.001 and 500 mg/kg, preferably between about 0.1 and 100 mg/kg.

As described above, the compounds of the present invention have enzyme-inhibiting properties. In particular, they inhibit the action of the natural enzyme renin. Renin passes from the kidneys into the blood where it effects the cleavage of angiotensinogen, releasing the decapeptide angiotensin I which is then cleaved in the lungs, the kidneys and other organs to form the octapeptide angiotensin II. The octapeptide increases blood pressure both directly by arterial vasoconstriction and indirectly by liberating from the adrenal glands the sodium-ion-retaining hormone aldosterone, accompanied by an increase in extracellular fluid volume which increase can be attributed to the action of angiotensin II. Inhibitors of the enzymatic activity of renin lead to a reduction in the formation of angiotensin I, and consequently a smaller amount of angiotensin II is produced. The reduced concentration of that active peptide hormone is a direct cause of the hypotensive effect of renin inhibitors.

The action of renin inhibitors may be demonstrated *inter alia* experimentally by means of *in vitro* tests, the reduction in the formation of angiotensin I being measured in various systems (human plasma, purified human renin together with synthetic or natural renin substrate).

Inter alia the following *in vitro* tests may be used:

Recombinant human renin (expressed in Chinese Hamster Ovary cells and purified using standard methods) at 7.5 nM concentration is incubated with test compound at various concentrations for 1 h at RT in 0.1 M Tris-HCl buffer, pH 7.4, containing 0.05 M NaCl, 0.5 mM EDTA and 0.05 % CHAPS. Synthetic peptide substrate Arg-Glu(EDANS)-Ile-His-Pro-Phe-His-Leu-Val-Ile_His_Thr-Lys(DABCYL)-Arg9 is added to a final concentration of 2 µM and increase in fluorescence is recorded at an excitation wave-length of 350 nm and at an emission wave-length of 500 nm in a microplate spectro-fluorimeter. IC50 values are calculated from percentage of inhibition of renin activity as a function of test compound concentration (Fluorescence Resonance Energy Transfer, FRET, assay). Compounds of the formula I, in this assay, preferably can show IC_{50} values in the range from 1 nM to 20 µM.

Alternatively, recombinant human renin (expressed in Chinese Hamster Ovary cells and purified using standard methods) at 0.5 nM concentration is incubated with test compound at various concentrations for 2 h at 37°C in 0.1 M Tris-HCl buffer, pH 7.4, containing 0.05 M NaCl, 0.5 mM EDTA and 0.05 % CHAPS. Synthetic peptide substrate Arg-Glu(EDANS)-Ile-His-Pro-Phe-His-Leu-Val-Ile_His_Thr-Lys(DABCYL)-Arg9 is added to a final concentration of 4 µM and increase in fluorescence is recorded at an excitation wave-length of 340 nm and at an emission wave-length of 485 nm in a microplate spectro-fluorimeter. IC50 values are calculated from percentage of inhibition of renin activity as a function of test compound concentration (Fluorescence Resonance Energy Transfer, FRET, assay). Compounds of the formula I, in this assay, preferably can show IC_{50} values in the range from 1 nM to 20 µM.

In another assay, human plasma spiked with recombinant human renin (expressed in Chinese Hamster Ovary cells and purified using standard methods) at 0.8 nM concentration is incubated with test compound at various concentrations for 2 h at 37°C in 0.1 M Tris/HCl pH 7.4 containing 0.05 M NaCl, 0.5 mM EDTA and 0.025% (w/v) CHAPS. Synthetic peptide substrate Ac-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn-Lys-[DY-505-X5] is added to a final concentration of 2.5 µM. The enzyme reaction is stopped by adding an excess of a blocking inhibitor. The product of the reaction is separated by capillary electrophoresis and quantified by spectrophotometric measurement at 505 nM wave-length. IC50 values are calculated from percentage of inhibition of renin activity as a function of test compound concentration.

Compounds of the formula I, in this assay, preferably can show IC_{50} values in the range from 1 nM to 20 μM.

In another assay, recombinant human renin (expressed in Chinese Hamster Ovary cells and purified using standard methods) at 0.8 nM concentration is incubated with test compound at various concentrations for 2 h at 37°C in 0.1 M Tris/HCl pH 7.4 containing 0.05 M NaCl, 0.5 mM EDTA and 0.025% (w/v) CHAPS. Synthetic peptide substrate Ac-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn-Lys-[DY-505-X5] is added to a final concentration of 2.5 μM. The enzyme reaction is stopped by adding an excess of a blocking inhibitor. The product of the reaction is separated by capillary electrophoresis and quantified by spectrophotometric measurement at 505 nM wave-length. IC50 values are calculated from percentage of inhibition of renin activity as a function of test compound concentration. Compounds of the formula I, in this assay, preferably show IC_{50} values in the range from 1 nM to 20 μM.

In animals deficient in salt, renin inhibitors bring about a reduction in blood pressure. Human renin may differ from the renin of other species. In order to test inhibitors of human renin, primates, e.g.,marmosets (Callithrix jacchus) may be used, because human renin and primate renin are substantially homologous in the enzymatically active region. *Inter alia* the following *in vivo* tests may be used:

Compounds of the formula I can be tested in vivo in primates as described in the literature (see for example by Schnell CR et al. Measurement of blood pressure and heart rate by telemetry in conscious, unrestrained marmosets. Am J Physiol 264 (Heart Circ Physiol 33). 1993: 1509-1516; or Schnell CR et al. Measurement of blood pressure, heart rate, body temperature, ECG and activity by telemetry in conscious, unrestrained marmosets. Proceedings of the fifth FELASA symposium: Welfare and Science. Eds BRIGHTON. 1993.

The following Examples, while representing preferred embodiments of the invention, serve to illustrate the invention without limiting its scope.

Abbreviations:

abs.	Absolute
Ac	acetyl
AcOEt	ethyl acetate

AcOH	acetic acid
aq	aqueous
Bz	benzyl
cc	concentrated
c-hexane	cyclohexane
DIBAL-H	diisobutylaluminium hydride
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Ether	diethylether
Et_3N	triethylamine
Et_2O	diethylether
EtOH	ethanol
Flow	flow rate
h	hour(s)
HMPA	hexamethylphosphoroamide
HOBt	1-hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
iPrOH	isopropanol
L	liter(s)
KHMDS	potassium hexamethyldisilazane
LC-MS	Liquid Chromatography/Mass Spectrometry
LDA	lithium diisopropylamine
Me	methyl
MeI	methyl iodide
MeOH	methanol
MesCl	methanesulfonyl chloride
Min	minute(s)
mL	milliliter
MS	Mass Spectrometry
NMM	4-methylmorpholine
NMR	Nuclear Magnetic Resonance
Pd/C	palladium on charcoal

Ph	phenyl
PyBOP	(benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate
RT	room temperature
TBAF	tetra-butylammonium fluoride
TBDMS-Cl	tert-butyldimethylsilyl chloride
TBDMS	tert-butyldimethylsilyl
TBME	tert-Butylmethylether
TEA	triethylamine
TEMPO	2,2,6,6,-tetramethyl-1-piperidinyloxy free radical
TFA	trifluoroacetic acid
THF	tetrahydrofurane
RP	reverse phase
Prep	Preparative
sat.	saturated
TLC	Thin Layer Chromatography
t_r	retention time

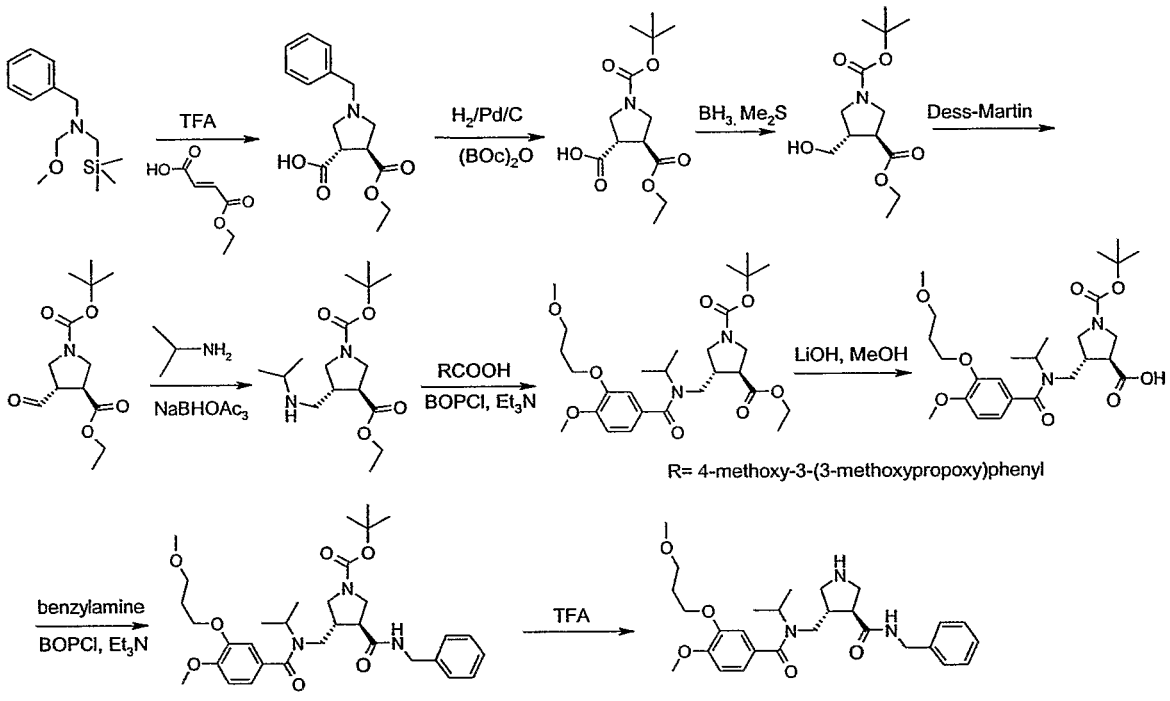
Trademarks

Celite	= Celite® (The Celite Corporation) = filtering aid based on diatomaceous earth
NH_2 Isolute	(= Isolute® NH_2, Isolute® is registered for Argonaut Technologies, Inc.) = ion exchanger with amino groups based on silica gel
Nucleosil	= Nucleosil®, trademark of Machery & Nagel, Düren, FRG for HPLC materials

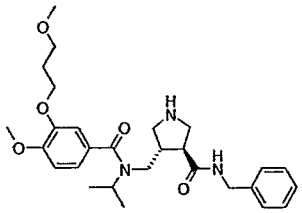
Temperatures are measured in degrees Celsius. Unless otherwise indicated, the reactions take place at RT.

TLC conditions: R_f values for TLC are measured on 5 x 10 cm TLC plates, silica gel F_{254}, Merck, Darmstadt, Germany.

Scheme 1



Example 1: (3S*,4S*)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-3-carboxylic acid benzylamide



To a solution of (3S*,4R*)-3-benzylcarbamoyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (61 mg, 0.098 mmol) in 2 mL CH_2Cl_2, TFA (113 µL, 1.46 mmol) is added. The mixture is stirred at 30°C for 2 h, then overnight at RT, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on an NH_2 Isolute SPE Flash column (eluent: CH_2Cl_2:MeOH 100:0 to 95:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.2. MS (LC-MS): 498 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.38 min.

To a solution of the free base in dioxane (2 mL), 4N HCl in dioxane (0.105 mmol, 26 µL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt as a white powder.

The starting material is prepared as follows:

A. (3S*,4S*)-1-Benzyl-pyrrolidine-3,4-dicarboxylic acid monoethyl ester

To a stirred solution of mono ethyl fumarate (2.85 g, 19.8 mmol) and trifluoroacetic acid (1.98 mmol, 0.15 mL) in methylene chloride (50 mL), N-benzyl-N-(methoxymethyl) trimethylsilyl amine (Aldrich) (9.41 g, 39.6 mmol) is added at 0°C under N_2. The mixture is stirred at 0°C for 30 min and then at RT over 48 h. The crude material is concentrated and purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 85:15 to 85:15 + 2% NH_4OH) to give the title compound. MS (LC-MS): 278.0 $[M+H]^+$. ^{1}H-NMR (CD_3OD, 400 MHz): δ = 1.29 (t, 3H), 3.28 (m, 5H), 3.60 (m, 1H), 4.07 (m, 2H), 4.20 (m, 2H), 7.47 (m, 5H) ppm.

B. (3S*,4S*)-Pyrrolidine-1,3,4-tricarboxylic acid 1-tert-butyl ester 3-ethyl ester

A mixture of (3S*,4S*)-1-benzyl-pyrrolidine-3,4-dicarboxylic acid monoethyl ester (10 g, 36.1 mmol), di-tert-butylcarbonate (7.9 g, 39.6 mmol) and $Pd(OH)_2$/C 20% (1 g, 50% wet) in EtOH (200 mL) is stirred under hydrogen atmosphere for 5 h. The crude material is filtered over a pad of Celite and concentrated. ^{1}H-NMR indicates that the title compound is obtained cleanly. TLC, R_f (AcOEt) = 0.17. MS (LC-MS): 286.1 $[M-H]^-$.

C. (3S*,4S*)-4-Hydroxymethyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butylester 3-ethyl ester

To a solution of (3S*,4S*)-pyrrolidine-1,3,4-tricarboxylic acid 1-tert-butyl ester 3-ethyl ester (10 g, 34.8 mmol) in THF (180 mL), a solution of borane dimethylsulfide complex (2N in THF, 24.4 mL, 48.7 mmol) is added slowly at -10°C. The mixture is stirred at -10°C for 20 min, then allowed to reach RT and further stirred for 4 h. MeOH is carefully added (exothermic!), and the mixture is concentrated under reduced pressure. MeOH is again added, and the mixture is concentrated. This operation is repeated 3 times, then the mixture is finally taken up into a saturated aqueous solution of $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH from 100:0 to 95:5) to give the title compound as product. TLC, Rf (AcOEt) = 0.52. MS (LC-MS): 174.1 $[M+H\text{-}Boc]^+$.

D. (3S*,4S*)-4-Formyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

To a well stirred mixture of (3S*,4S*)-4-hydroxymethyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butylester 3-ethyl ester (3.21 g, 11.74 mmol) and Dess-Martin periodinane (2.63 g, 11.74 mmol) in CH_2Cl_2 (30 mL), slowly wet CH_2Cl_2 (232 µL of water in 10 mL of CH_2Cl_2) is added. The clear solution becomes cloudy toward the end of wet CH_2Cl_2 addition. The mixture is diluted with Et_2O, then concentrated to a few mL of solvent by rotary evaporation. The residue is taken up in Et_2O and then washed with a 1:1 10% $Na_2S_2O_3$ saturated aqueous $NaHCO_3$, followed by H_2O and brine. The aqueous washings are back-extracted with Et_2O, and this organic layer is washed with H_2O and brine. The combined organic layers are dried with Na_2SO_4, filtered and concentrated. The crude mixture is used in the next step without further purification. TLC, R_f (c-hexane/AcOEt 8:2) = 0.2.

E. (3S*,4R*)-4-(Isopropylamino-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

A solution of (3S*,4S*)-4-formyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (2.87 g, 10.56 mmol) and isopropylamine (2.72 mL, 31.68 mmol) in 1,2-dichloroethane (150 mL) is stirred 25 min, before addition of $NaBH(OAc)_3$ (3.12 g, 14.78 mmol) follows. The solution is stirred for 4 h, then diluted with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The combined organic extracts are dried over Na_2SO_4 and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 80:20) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1.

F. (3S*,4R*)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

A mixture of (3S*,4R*)-4-(isopropylamino-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (2.58 g, 8.2 mmol), 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid (1.93 g, 8.04 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (2.3 g, 9.02 mmol) and triethylamine (4.57 µL, 32.81 mmol) in CH_2Cl_2 (50 mL) is refluxed for 2 h and then quenched by the addition of aqueous $NaHCO_3$ solution. The organic layer is separated, and the aqueous phase is extracted 3 times with AcOEt. The combined organic extracts are dried (Na_2SO_4), and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 50:50 to 0:100 and then AcOEt/MeOH 95:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. t_R (HPLC, C18 column, 10-

100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.76 min.

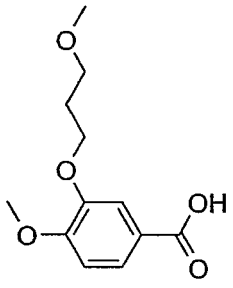
G. (3S*,4R*)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester

To a solution of (3S*,4R*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (1.41 g, 2.63 mmol) in MeOH (25 mL) cooled at 0°C, 662 mg of $LiOH \cdot H_2O$ is added. The reaction mixture is stirred overnight. The mixture is taken up in CH_2Cl_2, an aqueous HCl (5%) solution is added and the resulting mixture is extracted 3 times with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. The crude material is used in the next step without purification. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.15. MS (LC-MS): 409.0 $[M-H-Boc]^-$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.96 min.

H. (3S*,4R*)-3-Benzylcarbamoyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a stirring solution of (3S*,4R*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester (70 mg, 0.138 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (42 mg, 0.166 mmol) and triethylamine (77 µL, 0.552 mmol) in CH_2Cl_2 (3 mL), benzylamine (18 µL, 0.166 mmol) is added. The resulting solution is refluxed for 2 h and then quenched by the addition of aqueous $NaHCO_3$ solution. The organic layer is separated, and the aqueous phase is extracted 3 times with CH_2Cl_2. The combined organic extracts are dried (Na_2SO_4), and the solvent is removed *in vacuo*. The crude material is purified by preparative HPLC (C18-ODB-AQ, 5 µm, 20x50 mm, YMC, eluent: CH_3CN/H_2O + 0.1 % HCOOH flow: 20 mL/min). The HPLC fractions are collected and lyophilized to afford the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.2. MS (LC-MS): 598.0 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.60 min.

4-Methoxy-3-(3-methoxy-propoxy)-benzoic acid



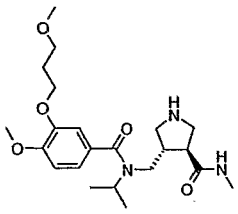
a. 4-Methoxy-3-(3-methoxy-propoxy)-benzoic acid methyl ester

A solution of methyl-3-hydroxy-4-methoxybenzoate (Aldrich) (89.3 g, 0.49 mol), K_2CO_3 (100.5 g, 0.727 mol) and 1-bromo-3-methoxy-propane (80 g, 0.523 mol) in CH_3CN (1100 mL) is refluxed for 6 h. After completion of the reaction, the mixture is cooled to RT and concentrated under reduced pressure. The residue is taken up into AcOEt (500 mL) and washed with water. The aqueous layer is back-extracted twice with AcOEt, and the combined organic extracts are dried over $MgSO_4$, filtered and concentrated to afford the title compound which is further used in the next step without purification. t_R (HPLC, CC 70/4 Nucleosil 3 C18HD column, 20 to 100% CH_3CN in H_2O in 2, then 4 min with 100% CH_3CN, CH_3CN and H_2O with 0.1% TFA, flow: 1.5 mL/min): 3.07 min.

b. 4-Methoxy-3-(3-methoxy-propoxy)-benzoic acid

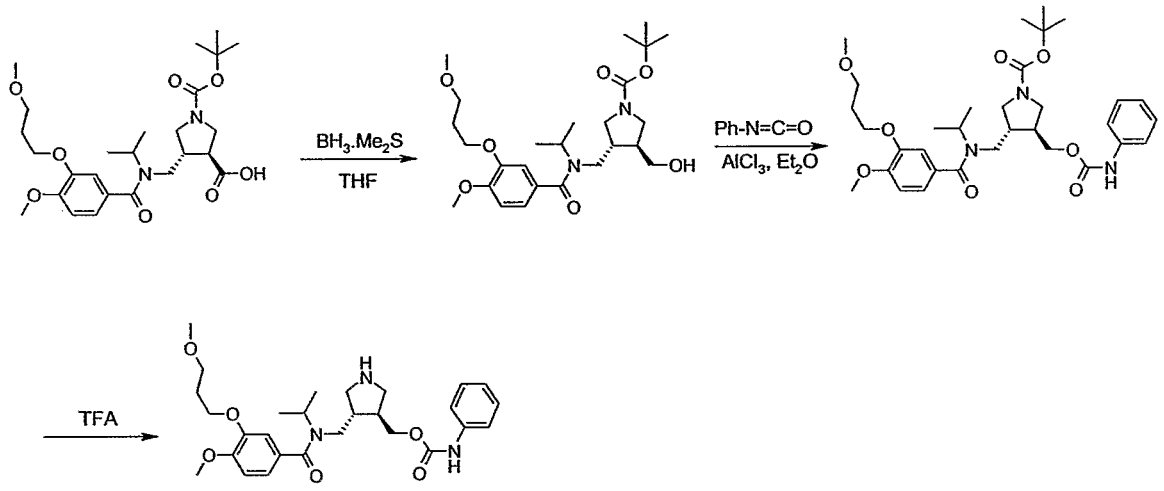
A solution of 4-methoxy-3-(3-methoxy-propoxy)-benzoic acid methyl ester (140 g, 0.55 mol) and NaOH (1N, 825 mL, 0.825 mol) in MeOH (840 mL) is stirred at RT for 18 h. After completion, the solvent is removed under reduced pressure, and the residue is diluted with water (200 mL) and extracted twice with AcOEt (250 mL). The aqueous layer is acidified by addition of aqueous HCl (2N, 470 mL) and extracted 3 times with AcOEt (1 L). The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude material is purified by crystallization in AcOEt to give the title compound. MS (LC-MS): 239.1 $[M-H]^-$; t_R (HPLC, CC 70/4 Nucleosil 3 C18HD column, 20 to 100% CH_3CN in H_2O in 2, then 4 min with 100% CH_3CN, CH_3CN and H_2O with 0.1% TFA , flow: 1.5 mL/min): 2.43 min.

Example 2: (3S*,4S*)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-3-carboxylic acid methylamide

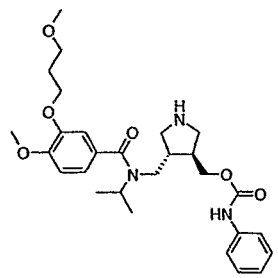


The title compound is prepared analogously as described for the title compound Example 1, starting from (3S*,4R*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester and methylamine. MS (LC-MS): 422.1 $[MH]^+$; t_R (HPLC, nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 3.83 min.

Scheme 2



Example 3: Phenyl-carbamic acid (3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester



To a solution of (3R*,4S*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-phenyl carbamoyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (68 mg,

0.11 mmol) in 2 mL CH_2Cl_2, TFA (128 µL, 1.66 mmol) is added. The mixture is stirred at 30°C for 2 h, then overnight at RT, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on Isolute SPE Flash NH_2 column (eluent: CH_2Cl_2/MeOH 100:0 to 97:3) to give the title product. MS (LC-MS): 514.0 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.52 min.

To a solution of the free base in dioxane (2 mL), 4N HCl in dioxane (0.099 mmol, 25 µL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt as a white powder.

The starting material is prepared as follows:

A. (3S*,4R*)-3-Hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

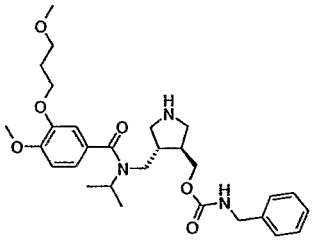
To a solution of (3S*,4R*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester (1.29 g, 2.54 mmol) (Example 1 G) in THF (25 mL), a solution of borane dimethylsulfide complex (2M in THF, 2.80 mL, 5.58 mmol) is slowly added at -10°C. The mixture is stirred for 20 min at -10°C, then allowed to reach RT and further stirred overnight. MeOH is carefully added (exothermic!), and the mixture is concentrated under reduced pressure. MeOH is again added, and the mixture is concentrated. This operation is repeated 3 times, and the mixture is finally taken up into a saturated aqueous solution of $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH from 100:0 to 95:5) to give the desired product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. MS (LC-MS): 395.1 [M+H-Boc]$^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.01 min.

B. (3R*,4S*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-phenyl carbamoyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

Phenyl isocyanate (44 µL, 0.404 mmol) followed by $AlCl_3$ (27 mg, 0.202 mmol) are added to a solution of (3S*,4R*)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-

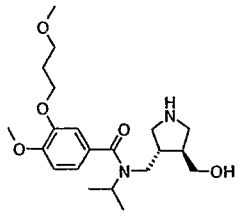
benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (100 mg, 0.202 mmol) in Et_2O (6 mL). The resulting mixture is stirred at RT overnight. For workup, a sat. solution of $NaHCO_3$ is added and the mixture is extracted with ethyl acetate. The combined extracts are dried (Na_2SO_4) and the solvent is evaporated. The crude product is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 80:20 to 0:100) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.5. MS (LC-MS): 514.0 $[M+H\text{-}Boc]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.91 min.

Example 4 : Benzyl-carbamic acid (3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester



The title compound is prepared analogously as described in Example 3 from (3S*,4R*)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and benzylisocyanate. MS (LC-MS): 528.3 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.52 min.

Example 5: N-((3S*,4S*)-4-Hydroxymethyl-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

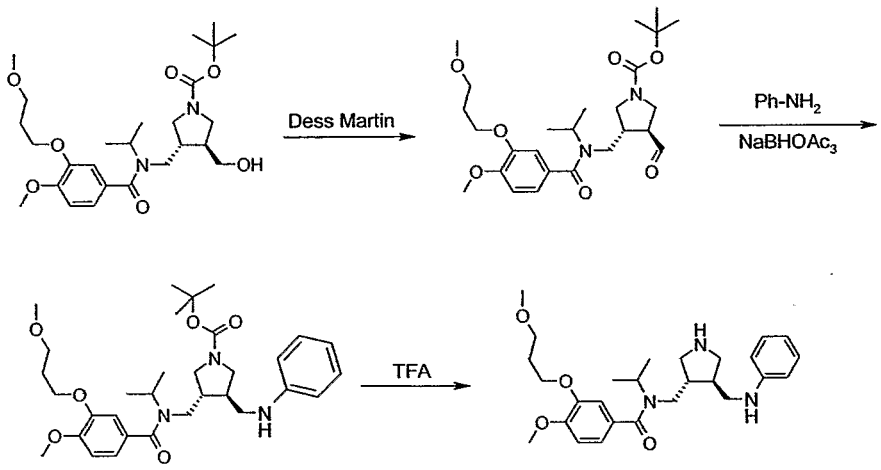


To a solution of (3S*,4R*)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (85 mg, 0.172 mmol) in 2 mL CH_2Cl_2, TFA (85 µL, 2.23 mmol) is added. The mixture is stirred 4.5 h at RT, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one

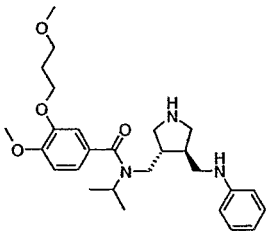
is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on Isolute SPE Flash NH_2 column (eluent: CH_2Cl_2/MeOH 100:0 to 99:1) to give the title product. MS (LC-MS): 395.1 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 3.75 min.

To a solution of the free base in dioxane (2 mL), 4N HCl in dioxane (0.009 mmol, 2.2 µL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt as a white powder.

Scheme 3



Example 6: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-((3S*,4S*)-4-phenylamino methyl-pyrrolidin-3-ylmethyl)-benzamide



To a solution of (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-phenylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (65 mg, 0.12 mmol) in 2 mL CH_2Cl_2, TFA (139 µL, 1.8 mmol) is added. The mixture is stirred 2 h at RT, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous

one is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on an Isolute SPE Flash NH_2 column (eluent: CH_2Cl_2/MeOH 100:0 to 97:3) to give the title product. TLC, R_f (SiO_2-NH_2, CH_2Cl_2/MeOH 95:5) = 0.6. MS (LC-MS): 470.0 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 3.37 min.

To a solution of the free base in dioxane (2 mL), (0.242 mmol, 60 µL) of 4N HCl in dioxane is added, and the resulting solution is lyophilized to afford the corresponding dihydrochloride salt as a white powder.

The starting material is prepared as follows:

A. (3S*,4R*)-3-Formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

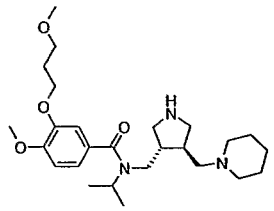
To a well-stirred mixture of (3S*,4R*)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (600 mg, 1.21 mmol) and Dess-Martin periodinane (272 mg, 1.21 mmol) in CH_2Cl_2 (10 mL), slowly wet CH_2Cl_2 (24 µL of water in 2 mL of CH_2Cl_2) is added. The clear solution becomes cloudy towards the end of wet CH_2Cl_2 addition. The mixture is diluted with Et_2O and concentrated to a few mL of solvent by rotary evaporation. The residue is taken up in Et_2O, and washed with a 1:1 10% $Na_2S_2O_3$ / saturated aqueous solution of $NaHCO_3$, followed by H_2O and brine. The aqueous washings are back-extracted with Et_2O, and this organic layer is washed with H_2O and brine. The combined organic layers are dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material is used without further purification in the next step. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.16 min.

B. (3R*,4R*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-phenylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (100 mg, 0.20 mmol) and aniline (26 µL, 0.28 mmol) in 1,2-dichloroethane (5 mL) is stirred 25 min, before the addition of $NaBH(OAc)_3$ (60 mg, 0.28 mmol) follows. The solution is stirred overnight at RT, then diluted

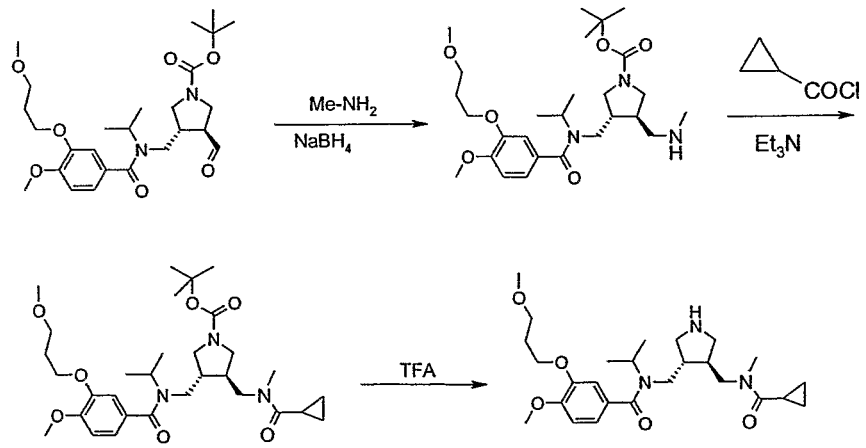
with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The combined organic extracts are dried over Na_2SO_4 and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 97:3) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.25. MS (LC-MS): 570.0 $[M+H]^+$; t_R (HPLC, nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.31 min.

Example 7 : N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-((3S*,4S*)-4-piperidin-1-ylmethyl-pyrrolidin-3-ylmethyl)-benzamide

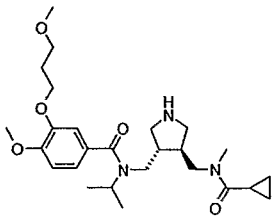


The title compound is prepared analogously as described in Example 5 from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and piperidine. MS (LC-MS): 462.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 3.74 min.

Scheme 4



Example 8: N-{(3S*,4S*)-4-[(Cyclopropanecarbonyl-methyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide



To a solution of (3R*,4R*)-3-[(cyclopropanecarbonyl-methyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (154 mg, 0.267 mmol) in 3 mL CH_2Cl_2, TFA (309 µL, 4.01 mmol) is added. The mixture is stirred 4 h at RT, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on Isolute SPE Flash NH_2 column (eluent: CH_2Cl_2 /MeOH 100:0 to 95:5) to give the title product. TLC, R_f (SiO_2-NH_2, CH_2Cl_2/MeOH 95:5) = 0.1. MS (LC-MS): 476.1 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.10 min.

To a solution of the free base in dioxane (2 mL), 4N HCl in dioxane (0.198 mmol, 50 µL) is added, and the resulting solution is lyophilized to afford the corresponding dihydrochloride salt as a white powder.

The starting material is prepared as follows:

A. (3R*,4R*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

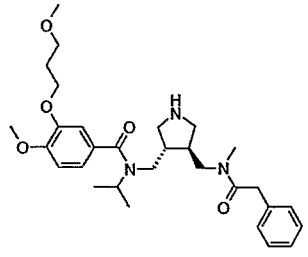
To a solution of (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (150 mg, 0.304 mmol) and magnesium sulfate (92 mg, 0.373 mmol) in THF (4 mL), methylamine (1.52 mL, 3.044 mmol, 2M in THF) is added. The solution is stirred at RT overnight under nitrogen atmosphere and $NaBH_4$ (23 mg, 0.608 mmol) is added. The resulting mixture is stirred for 1 h and the excess reducing agent quenched with water, CH_2Cl_2 is added and the reaction mixture is poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated and the aqueous phase extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and

concentrated in vacuo. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 95:5 +1% NH_4OH) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.05. MS (LC-MS) $[M-H]^+$ =508.1. t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 4.53 min.

B. (3R*,4R*)-3-[(Cyclopropanecarbonyl-methyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (134 mg, 0.264 mmol) in CH_2Cl_2 (2 mL), cyclopropanecarbonyl chloride (29 µL, 0.317 mmol) and triethylamine (44 µL, 0.317 mmol) are added under N_2 atmosphere. The mixture is stirred overnight at RT, diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous one is extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude product is used in the next step without purification. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.2. MS (LC-MS): 476.1 $[M+H\text{-}Boc]^+$. t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.42 min.

Example 9: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide



To a solution of (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (0.36 g, 0.575 mmol) in 12 mL CH_2Cl_2, TFA (0.664 mL, 8.62 mmol) is added. The mixture is stirred 2 h at 30°C, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one is back-extracted twice with CH_2Cl_2. The combined organic

extracts are dried over Na_2SO_4, filtered and concentrated. To a solution of the free base in dioxane (3 mL), 4N HCl in dioxane (0.144 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1. MS (LC-MS): 526.1 [M+H]+; t_R (Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.41 min.

The starting material is prepared as follows:

A. (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

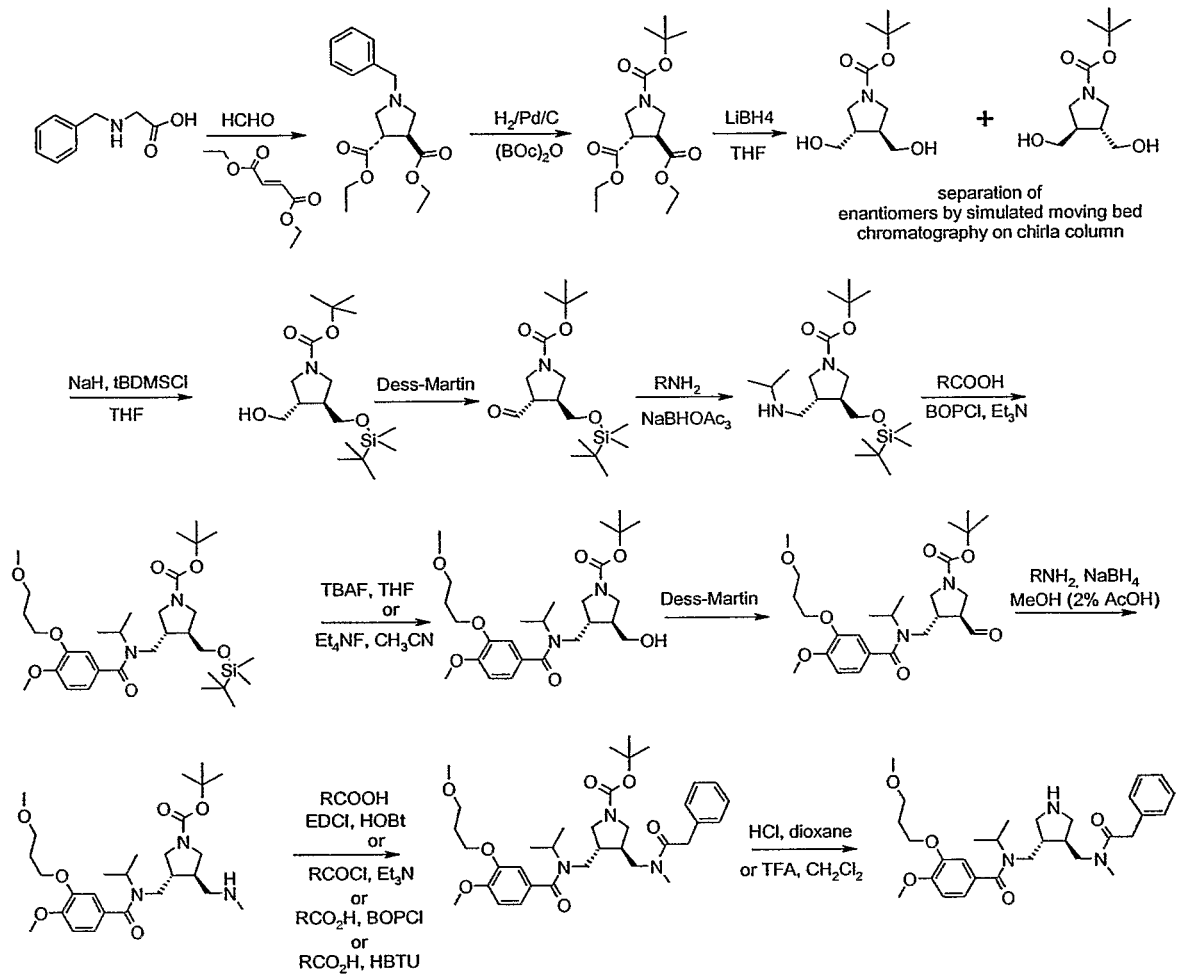
Racemic (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester is separated into the single enantiomers by preparative chiral HPLC on a Chiralpak AD-H column (4.6x250 mm, 5 µM particle size; flow rate 1 mL /min, UV = 210 nM, injection = 1.7 g in 5 mL ethanol and using ethanol as the eluent to give the enantiomerically pure title compound: t_R (HPLC, Chiralpak AD-H, HPLC 250X4.6 mm, ethanol, flow: 0.5 ml/min): 26.46 min; and (3S,4S)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester: t_R (HPLC, Chiralpak AD-H, HPLC 250X4.6 mm, ethanol, flow: 0.5 ml/min): 13.53 min.

B. (3R*,4R*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared from (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (79 mg, 0.165 mmol) and phenylacethyl chloride according to Example 8, reaction step B. R_f (CH_2Cl_2/MeOH 95:5) = 0.4. MS (LC-MS): 526.1 [M+H]+; t_R (Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.71 min.

Alternatively, the starting material (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester is prepared according to scheme 5 as follows:

Scheme 5



A. (3S*,4S*)-1-Benzyl-pyrrolidine-3,4-dicarboxylic acid diethyl ester

A mixture of N-benzylglycine (51.3 g, 310.55 mmol), diethylfumarate (51.85 mL, 316.76 mmol) and paraformaldehyde powder (10.25 g, 341.6 mmol) in toluene (500 mL) is heated at reflux for 2 h, while collecting water using a dean-stark apparatus. The solvent is concentrated and the mixture purified by distillation under vacuum (~50 mbar), the desired title compound distilling at 80-85°C. TLC, R_f (CH_2Cl_2/acetone 95:5) =0.56. MS (LC-MS): 306.2 $[M+H]^+$; t_R (HPLC, RP8 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.35 min.

B. (3S*,4S*)-Pyrrolidine-1,3,4-tricarboxylic acid 1-tert-butyl ester 3,4-diethyl ester

A mixture of (3S*,4S*)-1-benzyl-pyrrolidine-3,4-dicarboxylic acid diethyl ester (82.8 g, 271.14 mmol), di-tert-butylcarbonate (88.76 g, 406.71 mmol) and Pd/C 10% (8 g) in EtOH (1.5 L) is stirred under hydrogen atmosphere. The crude material is filtered over a pad of Celite and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/acetone 100:0 to 95:5). TLC, R_f (CH_2Cl_2/acetone 95:5) = 0.51. MS (LC-MS): 216.2 $[M+H\text{-}Boc]^+$.

C. (3S*,4S*)-3,4-Bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a ice-cooled solution of (3S*,4S*)-pyrrolidine-1,3,4-tricarboxylic acid 1-tert-butyl ester 3,4-diethyl ester (36 g, 114.15 mmol) in THF (1 L), is added dropwise a solution of $LiBH_4$ (228.3 mmol) in THF (250 mL). The reaction mixture is stirred overnight at room temperature and quenched with an aqueous solution of NaOH 2N (400 mL). Ether is added, the layers are separated and the aqueous one back extracted twice with ether. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated to give the title compound which is used without further purification in the next step. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.14. MS (LC-MS): 232.2 $[M+H]^+$; t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.37 min.

(3S,4S)-3,4-Bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3,4-Bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

The two enantiomers are separated via chiral preparative HPLC using simulated moving bed chromatography (SMB) "UOP SORBEX Prep." Technology with 16 columns "Princeton Chromatography Inc." (7.5 x 2.12 cm), stationary phase: Chiralpak AD Prep. 20 μm, (eluent: hexane/EtOH/MeOH 90:5:5).

(3S,4S)-3,4-Bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: t_R (Chiralpak AD-H, 250 x 4.6 mm, flow rate 1 mL /min) (eluent: hexane/EtOH 90:10): 6.4 min. $[\alpha]_D$ = -11.1 (c = 1.795, $CHCl_3$).

(3R,4R)-3,4-Bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: t_R (Chiralpak AD-H, 250 x 4.6 mm, flow rate 1 mL :min) (eluent: hexane/EtOH 90:10): 8.58 min. $[\alpha]_D$ = +10.2 (c = 1.795, $CHCl_3$).

D. (3S,4S)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a suspension of sodium hydride (60 % in oil, 0.996 g, 24.9 mmol) (previously washed with pentane) in THF (40 mL) is added dropwise under a nitrogen atmosphere a solution of (3S,4S)-3,4-bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (4.8 g, 20.75 mmol) in THF (40 mL) at 0°C. The mixture is stirred for 1.5 h at 0°C before the dropwise addition of a solution of tert-butyl(chloro)dimethylsilane (3.44 g, 22.83 mmol) in THF (40 mL). The resulting mixture is further stirred 1 h at 0°C and 1 h at RT, then poured into an aqueous solution of $NaHCO_3$ (5%) (150 mL) and extracted 3 times with Et_2O. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 99:1 to 93:7). TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.33. MS (LC-MS): 346.2 $[M+H]^+$.

E. (3S,4S)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a well stirred mixture of (3S,4S)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (8.2 g, 23.73 mmol) and Dess-Martin periodinane (10.06 g, 23.73 mmol) in CH_2Cl_2 (60 mL), slowly wet CH_2Cl_2 (0.47 mL of water in 60 mL of CH_2Cl_2) is added. The clear solution becomes cloudy toward the end of wet CH_2Cl_2 addition and is further stirred over-night. Then concentrated to a few mL of solvent by rotary evaporation and taken up in Et_2O. A solution of 1:1 10% $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ is added. The layers are separated and the organic extract is washed successively with H_2O and brine. The aqueous washings are back-extracted with Et_2O, and this organic layer is washed with H_2O and brine. The combined organic layers are dried with Na_2SO_4, filtered and concentrated. The crude mixture is used in the next step without further purification. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.42. MS (LC-MS): 244.2 $[M+H\text{-}Boc]^+$; t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 6.45 min.

F. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (3S,4S)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (7.7 g, 22.41 mmol) and isopropylamine (5.78 mL, 67.24 mmol) in 1,2-dichloroethane (200 mL) is stirred 25 min before the addition of $NaBH(OAc)_3$ (11.88 g, 56.03 mmol). The solution is stirred for 5 h, then diluted with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The aqueous layer is back extracted twice

with CH_2Cl_2 and the combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is used in the next step without further purification. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.39. MS (LC-MS): 387.2 $[M+H]^+$.

G. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of ((3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (8.9 g, 23.02 mmol), 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid (6.08 g, 25.32 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (6.45 g, 25.32 mmol) and triethylamine (7.62 mL, 92.07 mmol) in CH_2Cl_2 (230 mL) is refluxed for 3 h. The reaction is quenched by the addition of an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous phase is extracted 3 times with AcOEt. The combined organic extracts are dried (Na_2SO_4), and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/acetone 95:5 to CH_2Cl_2/MeOH 95:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.47. MS (LC-MS): 609.4 $[M+H]^+$; t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 7.05 min.

H. (3S,4R)-3-Hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (8.75 g, 14.37 mmol) in THF (50 mL) is added tetrabutylammonium fluoride trihydrate (6.8 g, 24.55 mmol) under a nitrogen atmosphere. The reaction mixture is stirred overnight. Water and AcOEt are added, the layers are separated and the aqueous one extracted twice with AcOEt. The combined organic extracts are dried (Na_2SO_4), and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 97:3 to 95:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. MS (LC-MS): 395.1 [M+H-Boc]+; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.01 min.

I. (3S,4R)-3-Formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound under E in Scheme 5 from (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.16 min.

J. (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (2.7 g, 5.48 mmol) in MeOH (containing 2% AcOH, 25 mL), methylamine (13.7 mL, 27.41 mmol, 2M in MeOH) is added. The solution is stirred at RT for 1 h under nitrogen atmosphere and cooled to 10°C, before the careful addition of $NaBH_4$ (0.415 g, 10.96 mmol) (exothermic !!). The resulting mixture is allowed to reach RT and stirred for 1.5 h. The excess reducing agent is quenched with water, AcOEt is added and the reaction mixture is poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated and the aqueous layer extracted twice with AcOEt, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material is used in the next step without further purification. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.05. MS (LC-MS) [M+H]+ = 508.1. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 4.53 min.

K. (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (2 g, 3.35 mmol) in CH_2Cl_2 (25 mL), phenylacetyl chloride (0.53 mL, 4.02 mmol) and triethylamine (0.56 mL, 4.02 mmol) are added under N_2 atmosphere at 0°C. The mixture is stirred 30 min at 0°C, then allowed to reach RT and further stirred for 1 h. The reaction mixture is diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous one is extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude product is purified by

flash chromatography on silica gel (eluent: c-hexane/AcOEt 20:80 to 0:100) to give the title compound. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.4. MS (LC-MS): 526 $[M-Boc+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.71 min.

In a similar fashion as described above for Example 9/reaction step J,

(3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

is prepared from racemic (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester by reductive amination with methylamine in presence of $NaBH_4$: TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.05. MS (LC-MS) [M+H]+ = 508.1. t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 4.53 min.

A. (3S*,4S*)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared in a similar manner as described for Example 9/reaction step D, from (3S*,4S*)-3,4-bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (25.0 g, 108 mmol), tert-butyl(chloro)dimethylsilane (17.9 g, 119 mmol) and NaH (3.11 g, 130 mmol; 55-65% dispersion in oil) in THF (0.6 L) as a yellowish oil. MS: 346.2 $[M+H]^+$.

B. (3S*,4S*)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared in a similar manner as described for Example 9/reaction step E, from (3S*,4S*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (10.4 g, 58.9 mmol) and Dess-Martin periodinane (25.0 g, 58.9 mmol) in CH_2Cl_2 (150 mL), slowly wet CH_2Cl_2 (1.17 mL of water in 150 mL of CH_2Cl_2) as colorless oil. MS: 244.2 $[M+H-Boc]^+$. t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 6.46 min.

C. (3S*,4R*)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared in a similar manner as described for Example 9/reaction step F, from (3S*,4S*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (19.3 g, 56.1 mmol), isopropylamine (14.5 mL, 168 mmol) and $NaBH(OAc)_3$ (29.7 g, 140 mmol) in 1,2-dichloroethane (0.5 L) as a yellowish oil. MS: 387.2 $[M+H]^+$. t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.34 min.

D. (3S*,4R*)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared in a similar manner as described for Example 9/reaction step G, from ((3S*,4R*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (22.9 g, 59.1 mmol), 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid (15.6 g, 65.1 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (16.6 g, 65.1 mmol) and triethylamine (19.6 mL, 237 mmol) in CH_2Cl_2 (0.6 L) as a yellowish oil. MS: 609.4 $[M+H]^+$; t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 7.06 min.

E. (3S*,4R*)-3-Hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

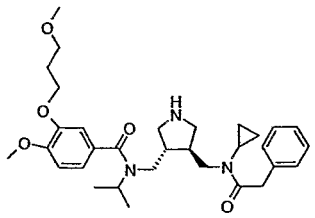
The title compound is prepared in a similar manner as described for Example 9/reaction step H, from (3S*,4R*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (25.0 g, 41.1 mmol) and tetrabutylammonium fluoride trihydrate (19.4 g, 61.6 mmol) in THF (150 mL) as a colorless oil. MS: 495.2 [M+H]+; t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.84 min.

F. (3S*,4R*)-3-Formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared in a similar manner as described for Example 9/reaction step I, from (3S*,4R*)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (4.9 g, 9.95 mmol) and Dess-Martin periodinane (4.22 g, 9.95 mmol) in CH_2Cl_2 (30 mL), slowly wet CH_2Cl_2 (0.20 mL of

water in 30 mL of CH_2Cl_2) as colorless oil. MS: 437.2 [M+H-BOC]+. t_R (HPLC, Nucleosil C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 4.99 min.

Example 10 : N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide



A solution of (3R,4R)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.32 g, 0.48 mmol) in a 4N HCl solution in dioxane (2.0 mL) is stirred at room temperature overnight. The reaction mixture is then freeze-dried to afford the corresponding hydrochloride salt as white solid. MS: 552.2 [M]+; t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.72 min.

The starting material is prepared as follows:

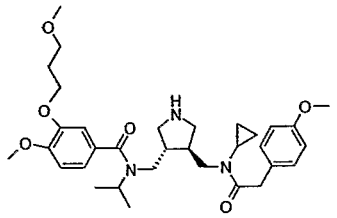
A. (3R,4R)-3-Cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (3S,4R)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (7.45 g, 15.1 mmol; Example 9 / reaction step I) and cycloproylamine (5.30 mL, 75.6 mmol) in MeOH (containing 2% AcOH, 90 mL) is stirred for 1 h at room temperature, followed by portionwise addition of NaBH4 (1.14 g, 30.2 mmol). After stirring for 1 h, the reaction mixture is concentrated to one third of its volume, water and a saturated NaHCO3 solution are added and the aqueous layer is extracted with AcOEt. The combined organics are dried (Na2SO4) and evaporated to dryness to afford the title compound as colorless oil. The crude material is used in the next step without further purification. MS (LC-MS) [M+H]+ = 534.2. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.79 min.

B. (3R,4R)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R,4R)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.30 g, 0.56 mmol) in CH2Cl2 (6 mL) are subsequently added Et3N (0.094 mL, 0.67 mmol), 1-hydroxy-benzotriazol hydrate (0.09 g, 0.67 mmol), N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (0.129 g, 0.67 mmol) and phenylacetic acid (0.09 g, 0.67 mmol), followed by stirring overnight. The reaction mixture is diluted with CH2Cl2 and then washed with 1N HCl (5 mL), saturated aqueous NaHCO3 and brine, the organic layer is dried over MgSO4 and concentrated. Purification by flash chromatography (eluent: hexane/AcOEt 25:75, then AcOEt 100%) gives the title compound as colorless oil. MS (LC-MS): 652.4 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.80 min.

Example 11 : N-[(3S*,4S*)-4-({Cyclopropyl-[2-(4-methoxy-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide



To a solution of (3R*,4R*)-3-({cyclopropyl-[2-(4-methoxy-phenyl)-acetyl]-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.17 g, 0.26 mmol) in dioxane (1 mL), 4N HCl in dioxane (0.647 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. TLC, R_f (CH_2Cl_2/MeOH 9:1 + 10 % NH_4OH) = 0.2. MS (LC-MS): 582.4 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.06 min.

The starting material is prepared as follows:

A. (3R*,4R*)-3-Cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

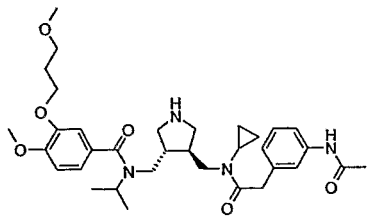
The title compound is prepared analogously as described for the title compound under J in Example 9 from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and cyclopropylamine. TLC, R_f (CH_2Cl_2/MeOH 9:1 + 10 % NH_4OH) = 0.48. MS (LC-MS): 534.4 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.53 min.

B. (3R*,4R*)-3-({cyclopropyl-[2-(4-methoxy-phenyl)-acetyl]-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of 4-methoxyphenylacetic acid (0.075 g, 0.45 mmol) in CH_2Cl_2 (3 mL), are added triethylamine (0.063 mL, 0.45 mmol), 1-hydroxy-benzotriazol hydrate (0.061 g, 0.45 mmol) and N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (EDC) (0.086 g, 0.45 mmol) followed by (3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.2 g, 0.375 mmol). The resulting mixture is stirred for 2 days at RT, then diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous one is extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude product is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 50:50 to 0:100) to give the title compound. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.35. MS (LC-MS): 682.4 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.77 min.

Alternatively, the coupling reaction is performed in a similar manner as described above using 1.1 equivalents of HOBt, EDC, NEt_3 and a mixture of DMF/THF 1:1.

Example 12 : N-[(3S*,4S*)-4-({[2-(3-Acetylamino-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide



To a solution of (3R*,4R*)-3-({[2-(3-acetylamino-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.31 g, 0.44 mmol) in dioxane (15 mL), 4N HCl in dioxane (6 mL) is added, the resulting solution is stirred at RT for 8h and then lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 609.1 $[M+H]^+$; t_R (HPLC, Macherey Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.03 min.

The starting material is prepared as follows:

A. (3R*,4R*)-3-({Cyclopropyl-[2-(3-nitro-phenyl)-acetyl]-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

At 0°C HBTU (426 mg, 1.12 mmol) is added to a solution of 3-nitrophenylacetic acid (187 mg, 1.03 mmol) in CH_3CN (10 mL) and the resulting solution is stirred for 10 min. Then a solution of (3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.2 g, 0.375 mmol). (500 mg, 0.94 mmol) and triethylamine (1.04 mL, 7.5 mmol) in CH_3CN (10 mL) is added at 0°C and the reaction mixture is stirred at RT for another 2 h. For workup a sat. solution of $NaHCO_3$ is added and the mixture is extracted with ethyl acetate. Washing of the combined extracts with brine, drying (Na_2SO_4), filtration and evaporation of the solvent affords the crude product which is purified by flash chromatography on silica gel (eluent: CH_2Cl_2 to CH_2Cl_2/MeOH 9:1) to give the title compound. MS (LC-MS): 597.0 $[M+H\text{-}Boc]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.47 min.

B. (3R*,4R*)-3-({[2-(3-Amino-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

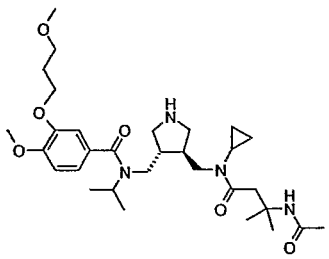
At RT H_2 is passed through a suspension of (3R*,4R*)-3-({cyclopropyl-[2-(3-nitro-phenyl)-acetyl]-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (660 mg, 0.95 mmol) and Raney-Ni (100 mg) for several hours. After completion of the reaction the mixture is filtered over Celite and the solvent is evaporated to give the title compound which is used without further purification. MS (LC-MS): 667.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.33 min.

C. (3R*,4R*)-3-({[2-(3-Acetylamino-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Triethylamine (67 µL, 0.48 mmol), DMAP (0.4 mg, 0.003 mmol) and acetic anhydride (46 µL, 0.48 mmol) are added to a solution of (3R*,4R*)-3-({[2-(3-amino-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (215 mg, 0.32 mmol) in THF (20 mL). The reaction mixture is stirred at RT for 16 h before water is added for workup. Extraction with ethyl acetate, drying of the combined extracts (Na_2SO_4), filtration and evaporation of the solvent affords the crude product which is purified by flash chromatography on silica gel (eluent: CH_2Cl_2 to CH_2Cl_2/MeOH 9:1) to give the title compound. MS (LC-MS): 709.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.04 min.

An alternative method for the N-Boc deprotection reaction is described in the following example:

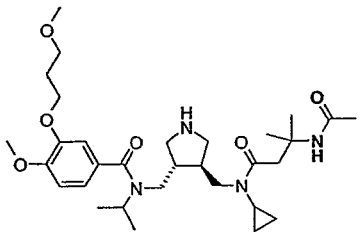
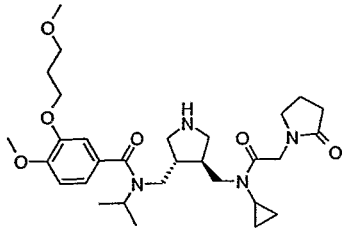
Example 13 : N-((3S,4S)-4-{[(3-Acetylamino-3-methyl-butyryl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

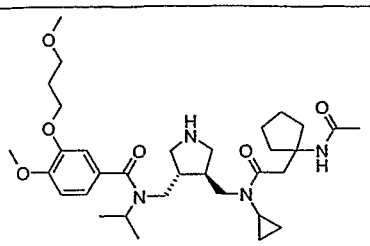
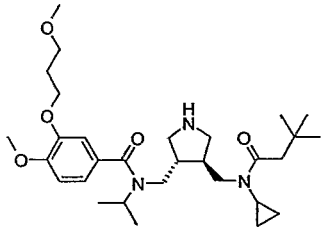
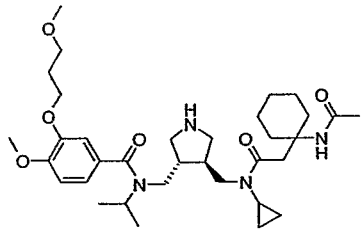
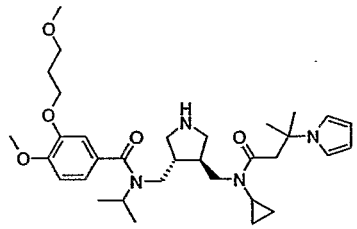
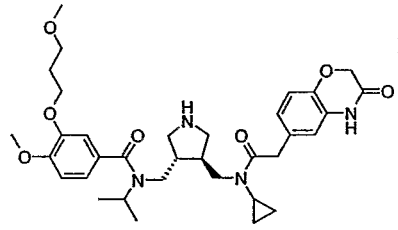
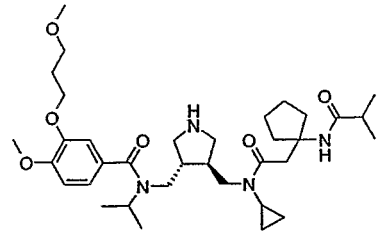


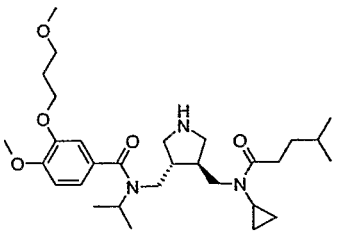
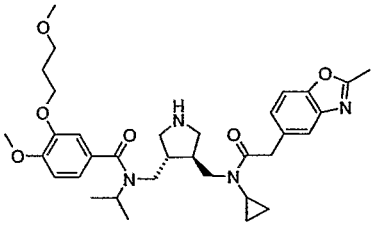
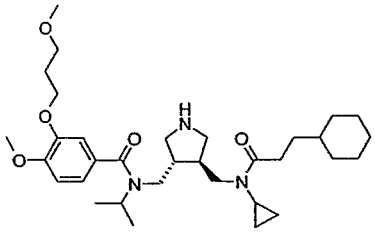
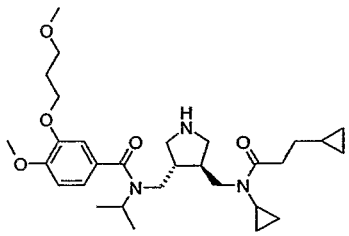
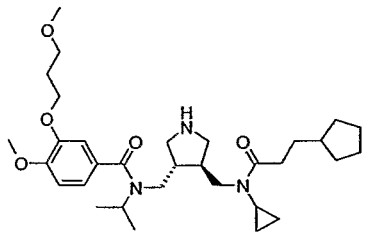
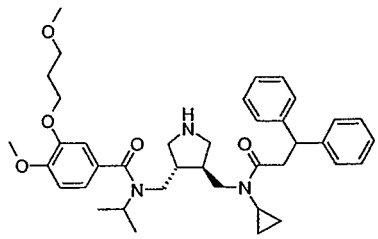
$ZnBr_2$ (110 mg, 0.49 mmol) is added to a solution of (3R,4R)-3-{[(3-acetylamino-3-methyl -butyryl)-cyclopropyl-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (150 mg, 0.22 mmol) in 1,2-dichloroethane (5 mL) and the resulting suspension is stirred at 55°C for 16h. In order to drive the reaction to completion another portion of $ZnBr_2$ (50 mg, 0.22 mmol) is added and heating is continued for another 24 h. For workup a sat. solution of $NaHCO_3$ is added and the mixture is extracted with CH_2Cl_2. Drying (Na_2SO_4) of the combined extracts, filtration and evaporation of the solvent affords the desired product as free base. The free base is dissolved in dioxane (2 mL) and fumaric acid (11 mg, 0.11 mmol) is added. Lyophilization yields the title compound as hemifumarate salt. MS (LC-MS): 575.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.90 min.

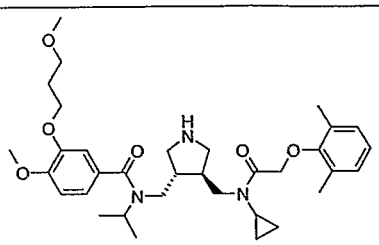
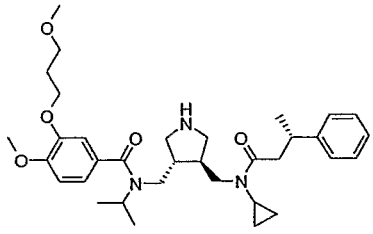
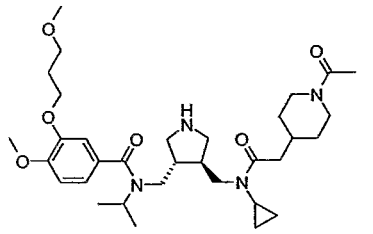
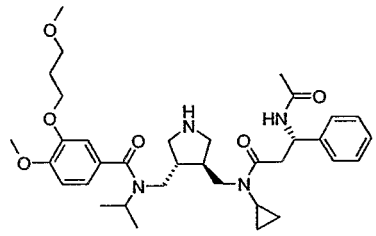
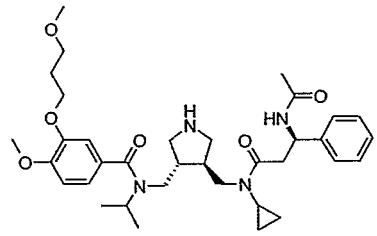
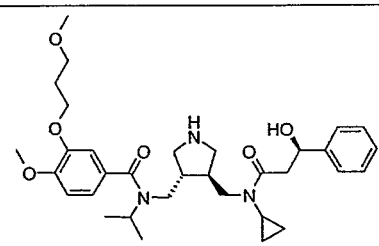
The following Examples are prepared according to the procedures described above in Examples 8, 9, 10, 11, 12 and 13:

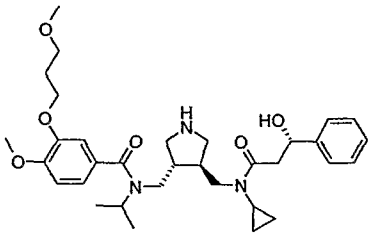
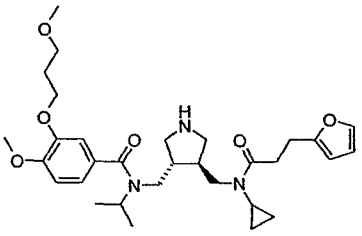
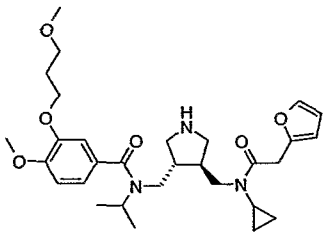
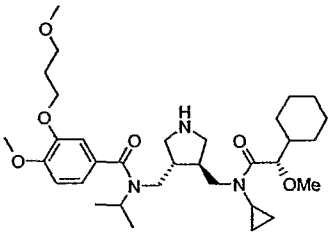
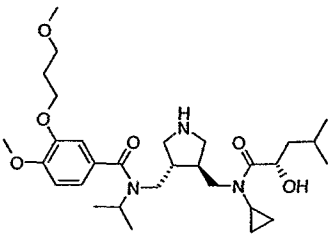
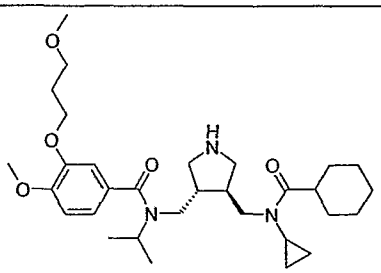
Table 1

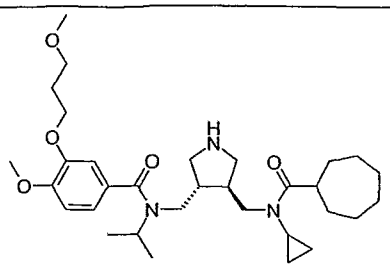
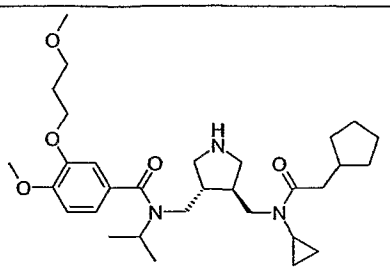
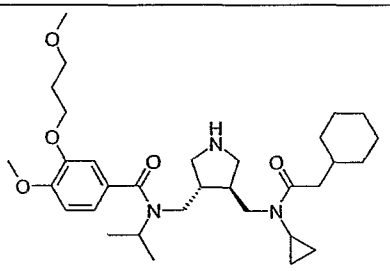
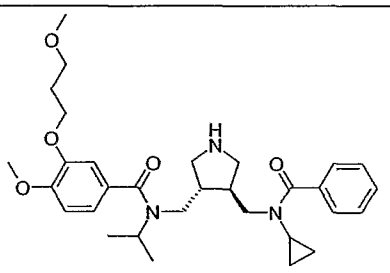
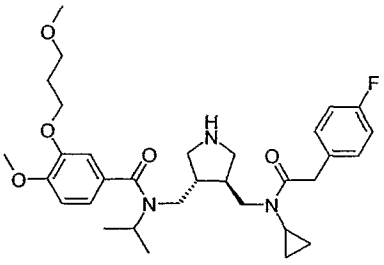
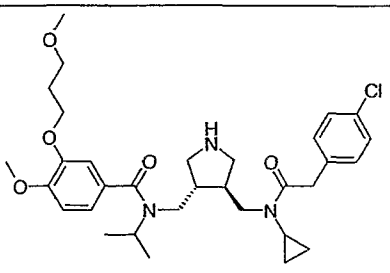
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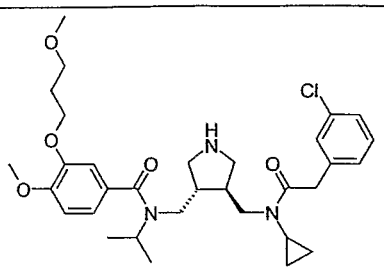
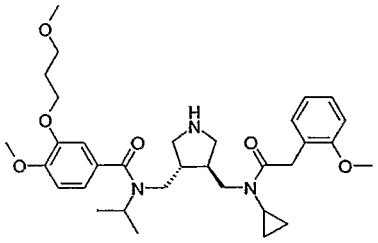
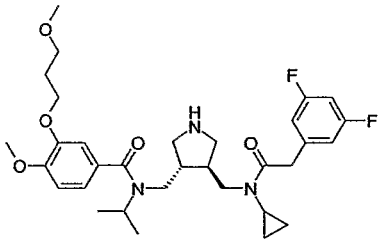
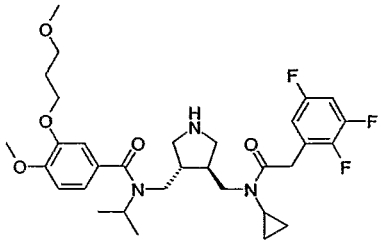
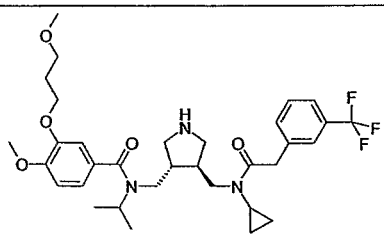
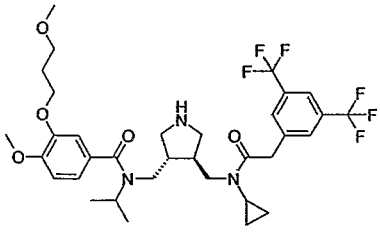
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18	(3S*, 4S*)		615.2	4.52[a]
19	(3S*, 4S*)		583.3	4.82[a]
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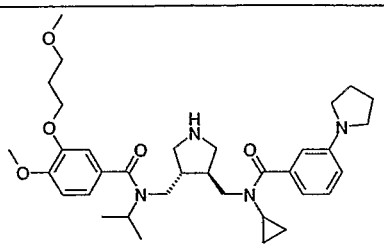
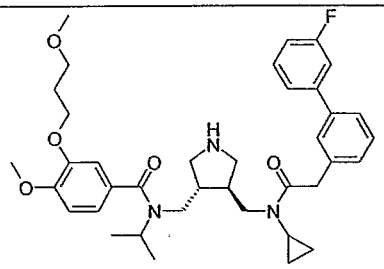
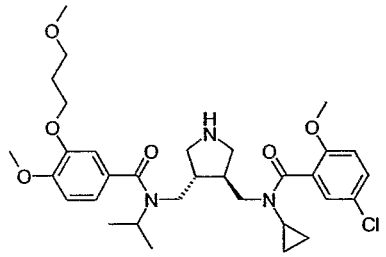
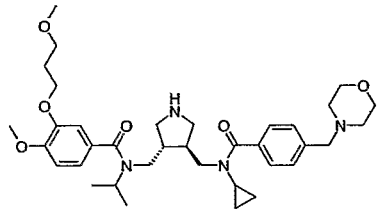
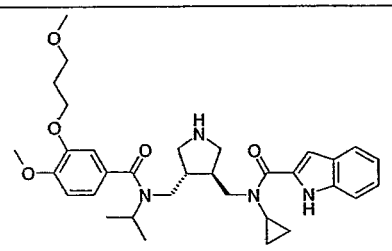
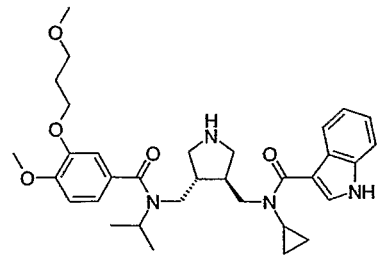
22	(3S*, 4S*)		532.3	5.12[a]
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25	(3S, 4S)		530.2	5.87[a]
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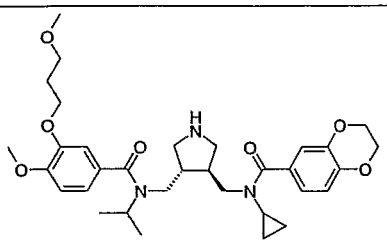
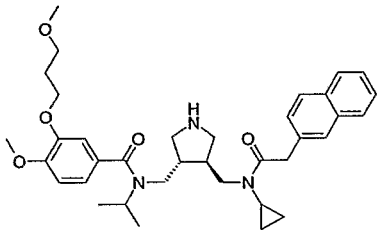
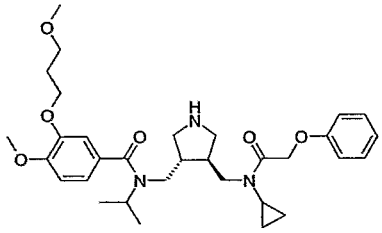
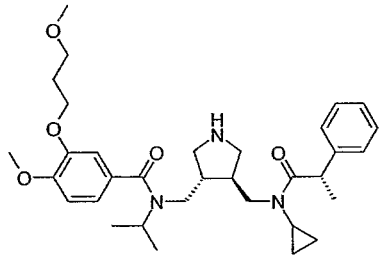
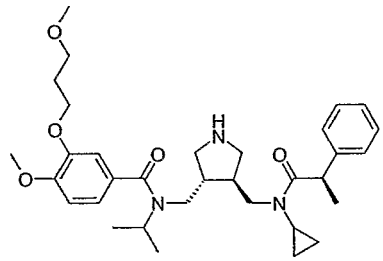
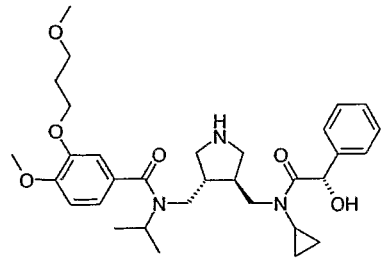
28	(3S, 4S)		596.3	5.44[a]
29	(3S, 4S)		580.0	4.95[a]
30	(3S, 4S)		601.5	3.04[b]
31	(3S, 4S)		623.5	0.36[b]
32	(3S, 4S)		623.5	0.35[b]
33	(3S, 4S)		582.2	4.46[a]

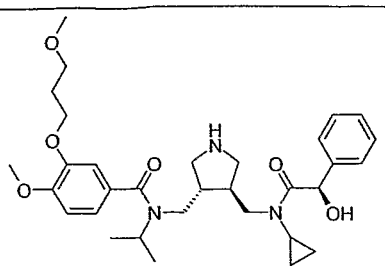
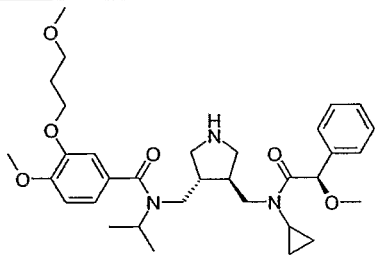
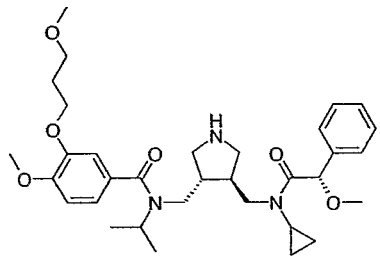
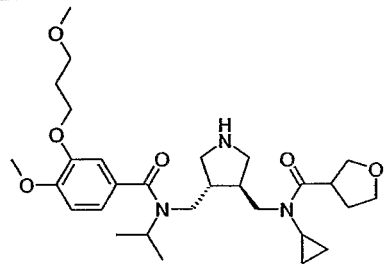
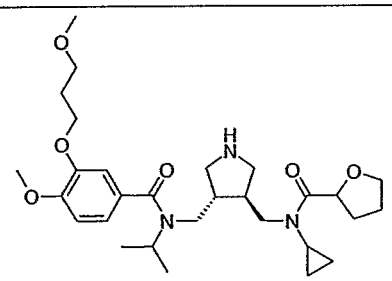
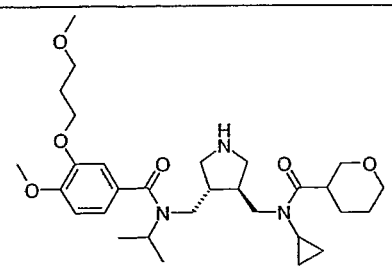
34	(3S, 4S)		582.2	4.50[a]
35	(3S, 4S)		556.3	4.67[a]
36	(3S, 4S)		542.2	4.48[a]
37	(3S, 4S)		588.3	2.89[c]
38	(3S, 4S)		548.2	2.41[d]
39	(3S*, 4S*)		544.4	4.69[e]

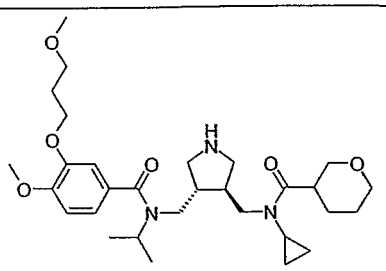
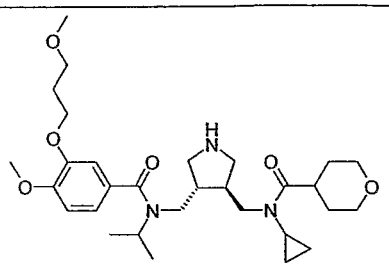
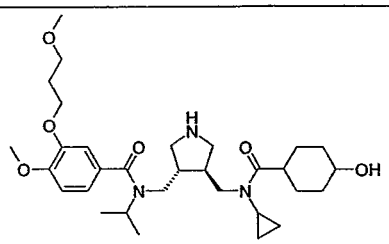
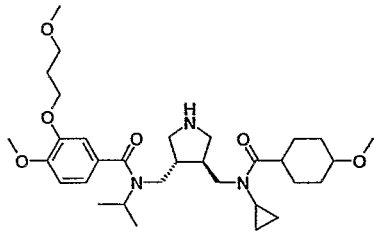
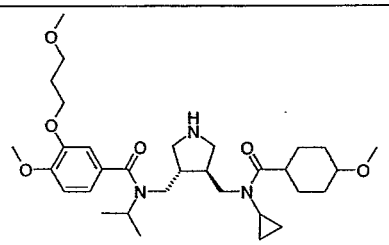
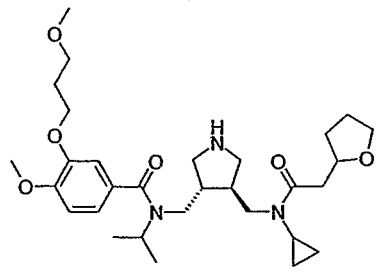
40	(3S,4S)		558.2	4.48[f]
41	(3S,4S)		544.3	4.97[e]
42	(3S*, 4S*)		558.4	5.28[e]
43	(3S*, 4S*)		538.2	4.61[e]
44	(3S*, 4S*)		570.2	4.85[e]
45	(3S,4S)		586.2	5.04[e]

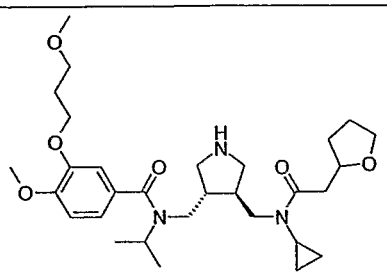
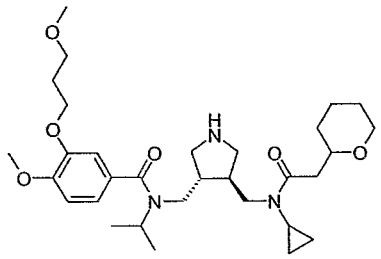
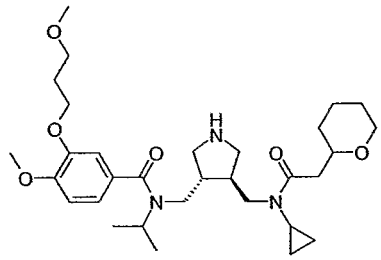
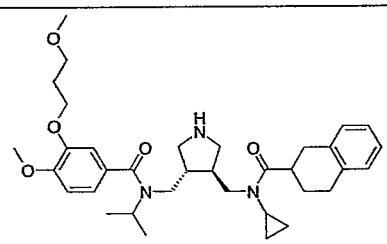
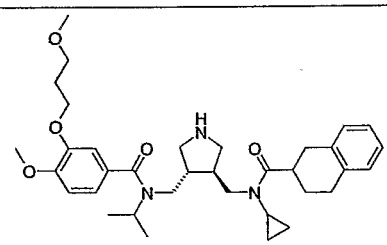
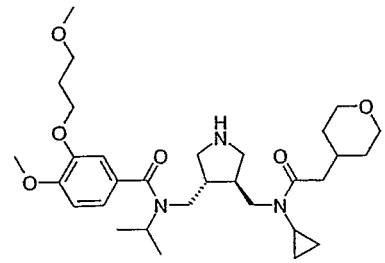
46	(3S*, 4S*)		587.3	4.79[e]
47	(3S*, 4S*)		582.3	4.58[e]
48	(3S*, 4S*)		588.2	4.36[f]
49	(3S*, 4S*)		606.2	4.99[e]
50	(3S*, 4S*)		620.2	4.67[f]
51	(3S*, 4S*)		688.2	5.58[e]

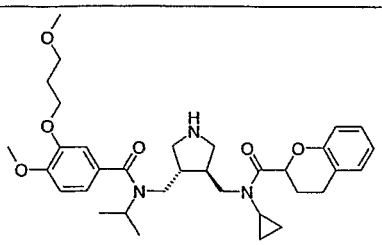
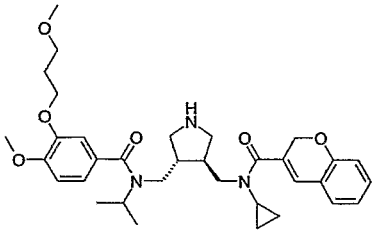
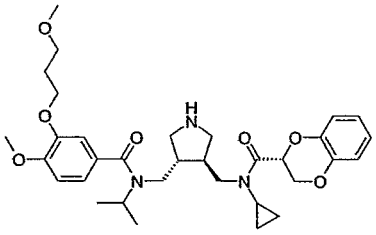
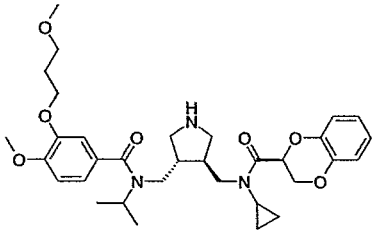
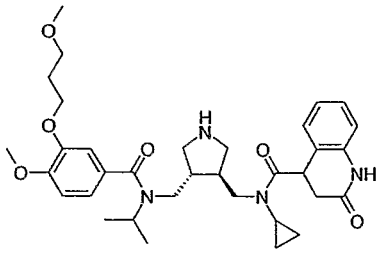
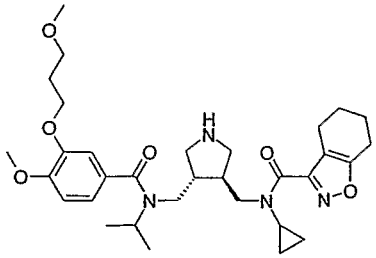
52	(3S*, 4S*)		607.4	3.96[e]
53	(3S*, 4S*)		646.4	5.18[e]
54	(3S*, 4S*)		602.2	4.30[f]
55	(3S*, 4S*)		637.3	2.93[f]
56	(3S*, 4S*)		577.3	4.91[e]
57	(3S*, 4S*)		577.3	4.54[e]

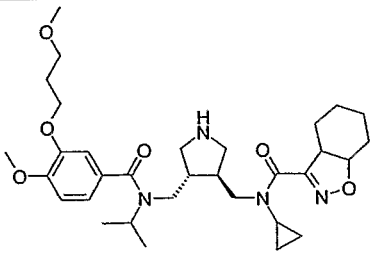
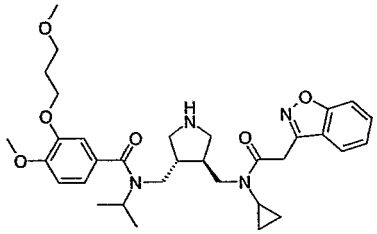
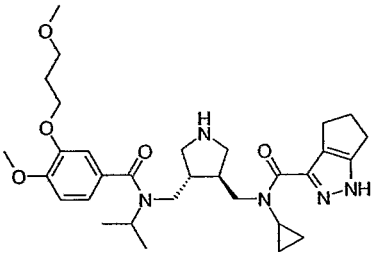
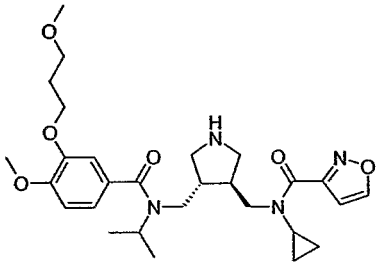
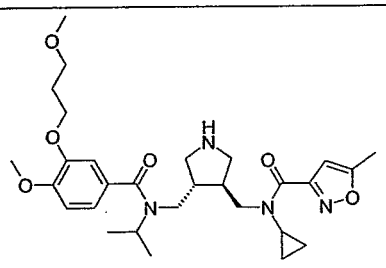
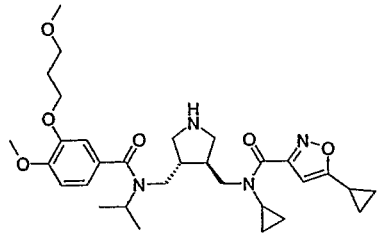
58	(3S,4S)		596.2	3.76[f]
59	(3S*, 4S*)		602.2	5.11[f]
60	(3S,4S)		568.2	4.04[f]
61	(3S*, 4S*)		566.4	4.96[e]
62	(3S*, 4S*)		566.4	4.92[e]
63	(3S,4S)		568.2	3.54[f]

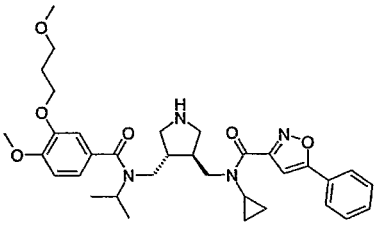
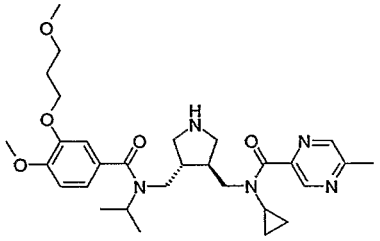
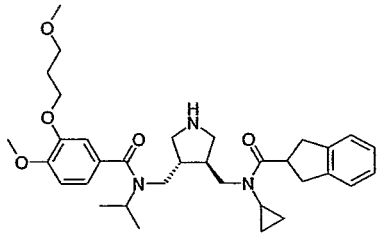
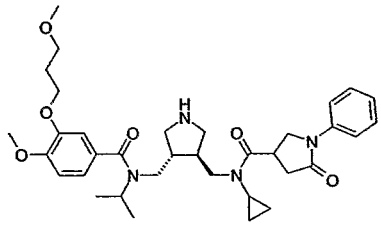
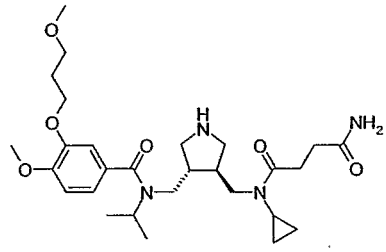
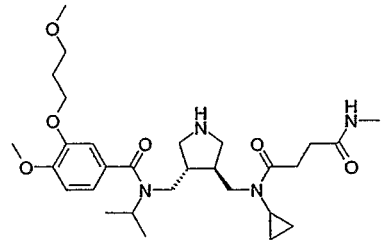
64	(3S,4S)		568.2	3.52[f]
65	(3S,4S)		582.2	3.78[f]
66	(3S,4S)		582.2	3.80[f]
67	(3S*,4S*)		532.2	3.29[f]
68	(3S*,4S*)		532.2	3.32[f]
69	(3S,4S)		546.2	3.40[f]

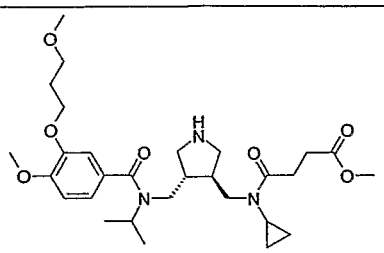
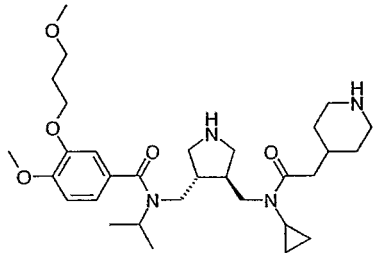
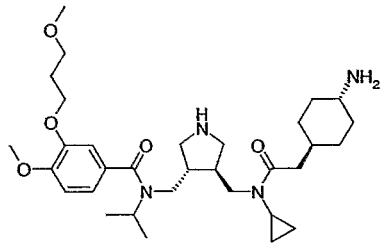
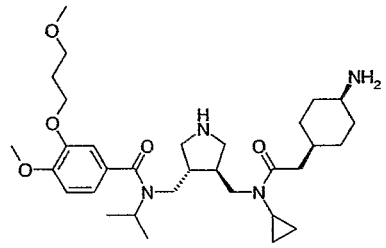
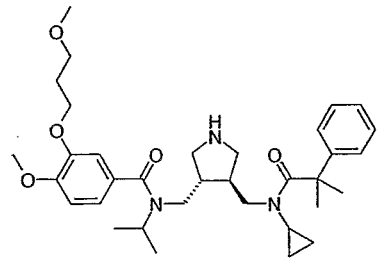
70	(3S,4S)		546.2	3.41[f]
71	(3S*, 4S*)		546.4	4.21[e]
72	(3S,4S)		560.2	3.10[f]
73	(3S,4S)		574.2	3.82[f]
74	(3S,4S)		574.2	3.60[f]
75	(3S,4S)		546.2	3.46[f]

76	(3S,4S)		546.2	3.48[f]
77	(3S,4S)		560.2	3.75[f]
78	(3S,4S)		560.2	3.72[f]
79	(3S,4S)		592.2	4.47[f]
80	(3S,4S)		592.2	4.46[f]
81	(3S*, 4S*)		560.4	4.08[e]

82	(3S,4S)		594.2	4.28[f]
83	(3S,4S)		592.2	4.20[f]
84	(3S,4S)		596.2	4.80[e]
85	(3S,4S)		596.2	4.80[e]
86	(3S,4S)		607.2	3.43[f] /3.50[f]
87	(3S,4S)		583.2	4.00[f]

88	(3S,4S)		585.3	4.73[e]
89	(3S,4S)		593.2	4.02[f]
90	(3S*, 4S*)		568.3	4.21[e]
91	(3S*, 4S*)		529.2	3.37[f]
92	(3S*, 4S*)		543.2	4.39[e]
93	(3S*, 4S*)		569.2	3.88[f]

94	(3S,4S)		605.2	4.97[e]
95	(3S*, 4S*)		554.2	4.15[e]
96	(3S,4S)		578.2	4.38[f]
97	(3S*, 4S*)		621.3	4.52[e]
98	(3S*, 4S*)		533.2	2.91[f]
99	(3S*, 4S*)		547.2	3.00[f]

100	(3S*, 4S*)		548.2	3.49[f]
101	(3S,4S)		559.4	3.75[e]
102	(3S,4S)		573.4	3.81[e]
103	(3S,4S)		573.4	3.81[e]
104	(3S,4S)		580.2	4.35[f]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 10-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[c] t_R (Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[d] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[e] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[f] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

The starting materials are prepared as follows:

For Examples 73 and 74: (3R,4R)-3-{[Cyclopropyl-cis-(4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-trans-(4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.77 g) on a Chiralpak AD (20 µM; column 50x500 mm) using n-hexane/isopropanol 4:1 as eluent (flow rate: 100 mL/min, UV 210 nm).

For Examples 75 and 76: (3R,4R)-3-{[Cyclopropyl-(2-tetrahydro-furan-2(R)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(2-tetrahydro-furan-2(S)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.34 g) on a Chiralpak AD (20 µM; column 50x500 mm) using n-hexane/EtOH/MeOH 70:25:5 as eluent (flow rate: 100 mL/min, UV 210 nm).

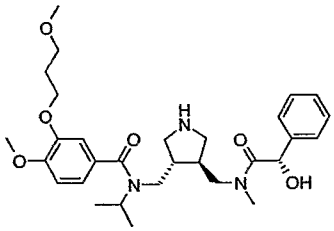
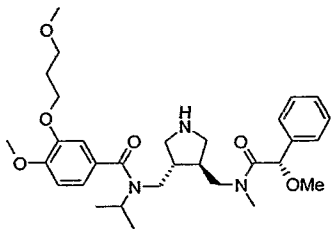
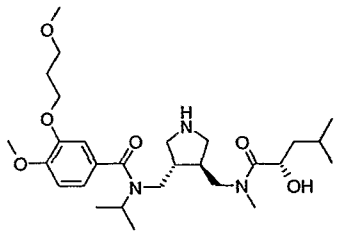
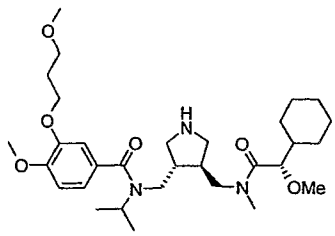
For Examples 77 and 78: (3R,4R)-3-{[Cyclopropyl-(2-tetrahydro-pyran-2(R)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(2-tetrahydro-pyran-2(S)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.32 g) on a Chiralpak AD (20 µM; column 50x500 mm) using a gradient n-hexane/EtOH 90:10 to 85:15 (after 30 min) as eluent (flow rate: 120 mL/min, UV 210 nm).

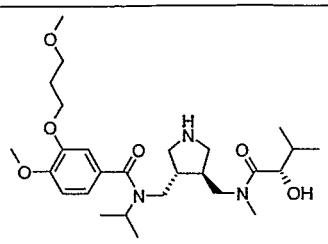
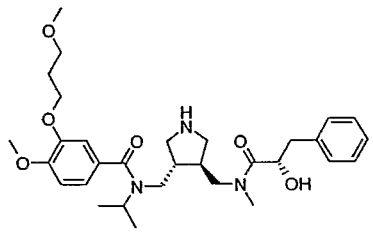
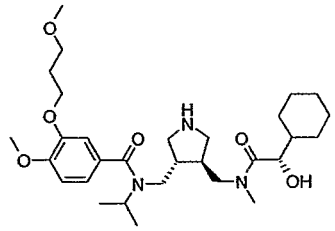
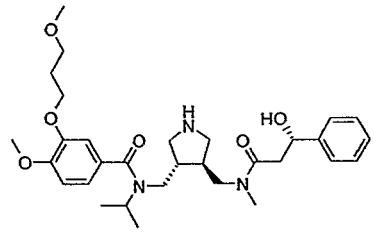
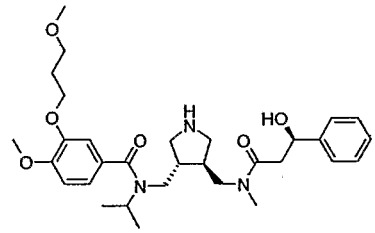
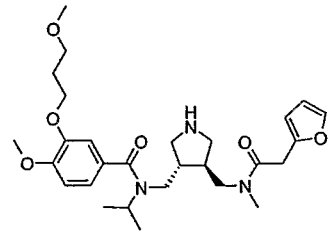
For Examples 79 and 80: (3R,4R)-3-{[Cyclopropyl-(1,2,3,4-tetrahydro-naphthalene-2(R)-carbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(1,2,3,4-

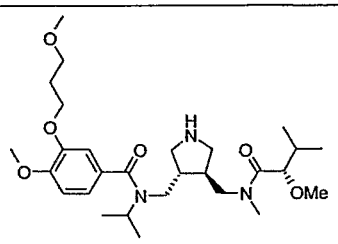
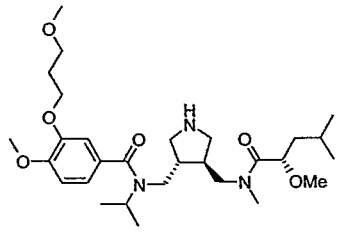
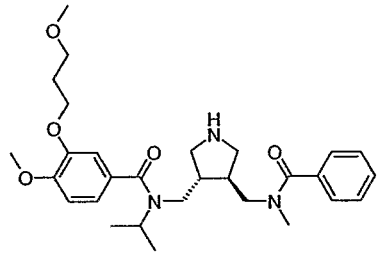
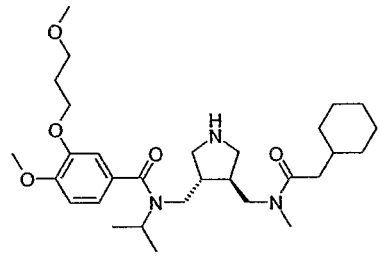
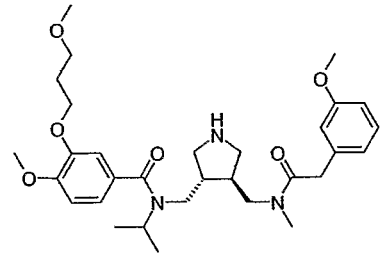
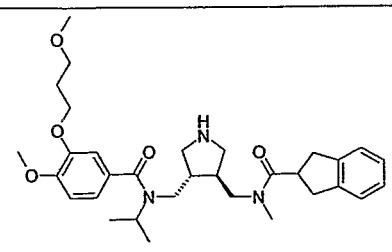
tetrahydro-naphthalene-2(S)-carbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.42 g) on a Chiralpak AD (20 µM; column 50x500 mm) using n-hexane/EtOH 4:1 as eluent (flow rate: 50 mL/min, UV 210 nm).

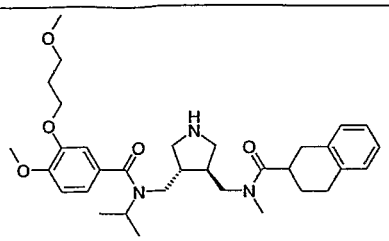
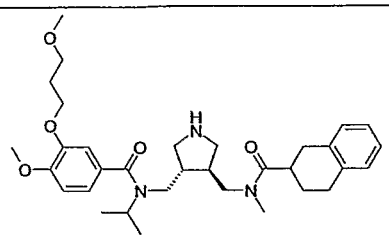
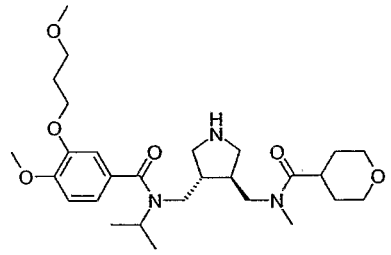
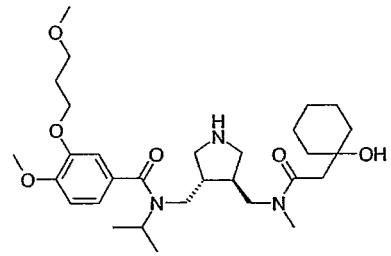
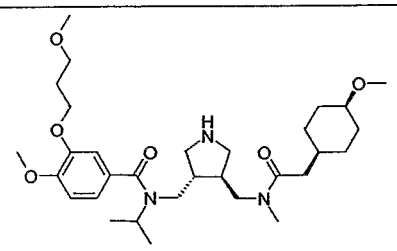
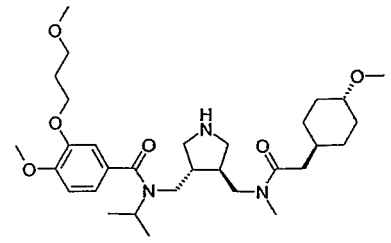
The following Examples are prepared according to the procedures described above in Examples 8, 9, 10, 11, 12 and 13:

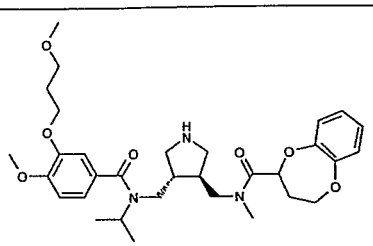
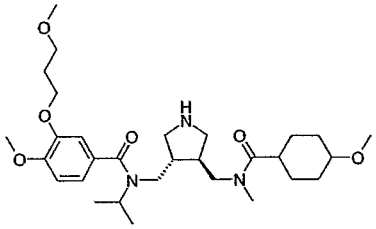
Table 2

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
105	(3S, 4S)		542.2	4.29[a]
106	(3S, 4S)		556.3	4.43[a]
107	(3S, 4S)		522.2	3.48[d]
108	(3S, 4S)		562.3	2.83[c]

109	(3S, 4S)		508.3	2.59[c]
110	(3S, 4S)		556.3	2.17minb[c]
111	(3S, 4S)		548.3	2.79[c]
112	(3S, 4S)		556.3	1.98[b]
113	(3S, 4S)		556.3	1.77[b]
114	(3S, 4S)		516.3	2.60[c]

115	(3S, 4S)		522.3	1.75[b]
116	(3S, 4S)		536.3	2.39[b]
117	(3S*, 4S*)		512.2	4.09[e]
118	(3S, 4S)		532.4	4.86[e]
119	(3S*, 4S*)		556.3	4.29[e]
120	(3S,4S)		552.2	4.04[f]

121	(3S,4S)		566.2	4.16[f]
122	(3S,4S)		566.2	4.17[f]
123	(3S*, 4S*)		520.3	3.74[e]
124	(3S,4S)		548.2	3.63[f]
125	(3S,4S)		562.3	3.55[f]
126	(3S,4S)		562.2	3.47[f]

127	(3S,4S)		584.3	5.11[f]
128 129	(3S,4S)		548.2	3.25[f] 3.41[f]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[c] t_R (Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[d] t_R (Nucleosil C18 HD column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[e] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[f] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

The starting materials are prepared as follows:

For Examples 121 and 122: (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-{[methyl-(1,2,3,4-tetrahydro-naphthalene-2(R)-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-{[methyl-(1,2,3,4-tetrahydro-naphthalene-2(S)-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.32 g) on a Chiralpak AD (20 µM, column 50x500 mm) using n-hexane/EtOH 1:1 as eluent (flow rate: 50 mL/min, UV 210 nm).

For Examples 128 and 129: (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-{[cis-(4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-

pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-{[trans-(4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.32 g) on a Chiralpak AD (20 μM, column 50x500 mm) using n-hexane/EtOH 1:1 as eluent (flow rate: 50 mL/min, UV 210 nm).

The following intermediates are prepared accordingly:

3-Acetylamino-3-methyl-butyric acid

Triethylamine (1.8 mL, 12.8 mmol), acetic anhydride (1.2 mL, 12.8 mL) and DMAP (10 mg, 0.09 mmol) are subsequentially added to a suspension of 3-amino-3-methyl-butyric acid (1.00 g, 8.5 mmol) in THF (100 mL). After heating at 60°C for 3 h AcOEt is added and the organic phase is washed with 1N HCl. Drying (Na_2SO_4), filtration and evaporation of the solvent yields the desired product. MS (LC-MS): $[M+H]^+$= 160.1. t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.40 min.

(1-Acetylamino-cyclopentyl)-acetic acid

Triethylamine (1.2 mL, 8.4 mmol), acetic anhydride (0.8 mL, 8.4 mL) and DMAP (10 mg, 0.09 mmol) are subsequentially added to a suspension of (1-amino-cyclopentyl)-acetic acid (1.00 g, 5.6 mmol) in THF (30 mL). After heating at 60°C for 2 h AcOEt is added and the organic phase is washed with 1N HCl. Drying (Na_2SO_4), filtration and evaporation of the solvent yields the desired product. MS (LC-MS): $[M+H]^+$= 186.1. t_R (HPLC, Waters Symmetry C18 column, 80-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.53 min.

(1-Acetylamino-cyclohexyl)-acetic acid

The title compound is prepared analogously as described for (1-acetylamino-cyclopentyl)-acetic acid from (1-amino-cyclohexyl)-acetic acid. MS (LC-MS): $[M+H]^+$= 200.1. (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.81 min.

(1-Isobutyrylamino-cyclopentyl)-acetic acid

The title compound is prepared analogously as described for (1-acetylamino-cyclopentyl)-acetic acid from (1-amino-cyclopentyl)-acetic acid. MS (LC-MS): $[M+H]^+$= 214.2. t_R (HPLC,

Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 3.08 min.

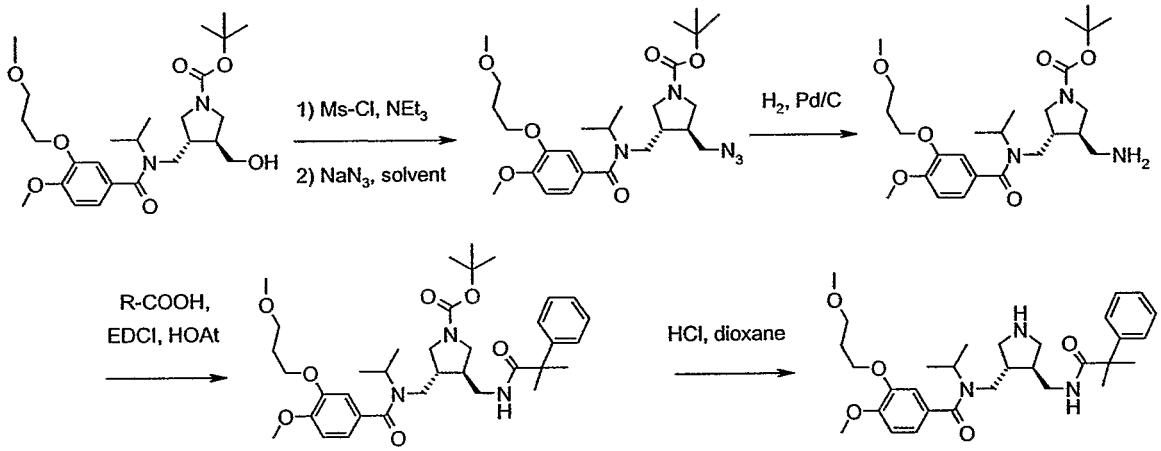
(S)-3-Acetylamino-3-phenyl-propionic acid

The title compound is prepared analogously as described for (1-acetylamino-cyclopentyl)-acetic acid from (S)-3-amino-3-phenylpropionic acid. MS (LC-MS): $[M+H]^+$= 208.2. t_R (HPLC, Waters Symmetry C18 column, 10-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.79 min.

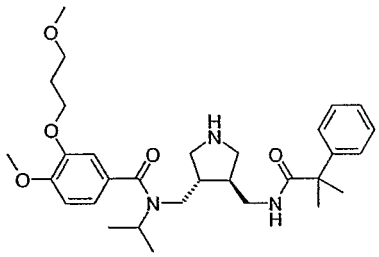
(R)-3-Acetylamino-3-phenyl-propionic acid

The title compound is prepared analogously as described for (1-acetylamino-cyclopentyl)-acetic acid from (R)-3-amino-3-phenylpropionic acid. MS (LC-MS): $[M+H]^+$= 208.2. t_R (HPLC, Waters Symmetry C18 column, 10-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 1.16 min.

Scheme 6



Example 130: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-{(3S,4S)-4-[(2-methyl-2-phenyl-propionylamino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide



The title compound is prepared according to Scheme 6 as follows: The solution of (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(2-methyl-2-phenyl-propionylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (227 mg, 0.319 mmol) in 4N HCl in dioxane (2 mL) is stirred for 6 hrs at room temperature. The volatiles are removed by freeze-drying to give the title compound as white solid. MS $[M+H]^+$ = 540.2. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.91 min.

The starting material is prepared as follows:

A. (3R,4S)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (2.32 g, 4.69 mmol; Example 10, reaction step H) is subsequently added at -20°C with stirring NEt_3 (1.95 mL, 14.1 mmol) and in a dropwise fashion methane sulfonylchloride (0.423 mL, 5.39 mmol). Stirring is continued for 20 min at -20 °C, the mixture is then diluted with CH_2Cl_2 and the organic layer is washed with 2N HCl, dried (Na_2SO_4) and evaporated to dryness to give the crude title compound as yellowish oil. TLC, R_f (hexane/AcOEt 1:3) = 0.13.

B. (3S,4R)-3-Azidomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R,4S)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (2.7 g, 4.71 mmol) in DMF (20 mL) is added in one portion NaN_3 (774 mg, 11.8 mmol) and the mixture is stirred at 70 °C overnight. After cooling to room temperature, a saturated aqueous $NaHCO_3$ solution is added, followed by extraction with diethyl ether. The combined organics are washed with brine, dried over Na_2SO_4 and concentrated. The crude product is purified by RP-HPLC on a PrepC_{18} OBD column (dimensions: 30x100 mm; 5 μM particle size, SunFire Ltd) and using a 95-5% gradient of MeCN/H_2O 5:95 (containing 0.1% TFA) to MeCN/H_2O

95:5 (containing 0.1% TFA) over 20 min gives the title compound as colorless oil. TLC, R_f (hexane/AcOEt 1:3) = 0.31. MS: 520.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.04 min.

C. (3R,4R)-3-Aminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (3S,4R)-3-azidomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.86 g, 3.58 mmol) in MeOH (40 mL) is hydrogenated overnight in the presence of Pd/C 10% (0.6 g; Engelhard 4505) at room temperature under atmospheric pressure to give, after filtration and drying in vacuo, the title compound as colorless oil. MS: 494.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.73 min.

D. (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(2-methyl-2-phenyl-propionylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R,4R)-3-aminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (200 mg, 0.405 mmol) and α,α-dimethylphenylacetic acid (101 mg, 0.608 mmol) in CH_2Cl_2 (3 mL) is subsequently added Et_3N (0.085 mL, 0.608 mmol), 1-hydroxy-7-azabenzotriazole (84 mg, 0.608 mmol; commercially available from ABCR, AV24631) and N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide HCl (118 mg, 0.608 mmol). Stirring is continued overnight at room temperature, the mixture is then diluted with CH_2Cl_2, and the organic layer is subsequently washed with 2N HCl, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Purification by RP-HPLC on a PrepC_{18} OBD column (dimensions: 30x100 mm; 5 µM particle size, SunFire Ltd) and using a 95-5% gradient of MeCN/H_2O 5:95 (containing 0.1% TFA) to MeCN/H_2O 95:5 (containing 0.1% TFA) over 20 min gives the title compound as colorless oil. MS $[M]^+$ = 640.2. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.2 min.

In a similar manner as described in Example 9 for the reaction step J, the following starting materials are prepared, which are used for the preparation of the Examples 137-148 listed in Table 3:

N-((3S*,4R*)-4-Ethylaminomethyl-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide: The title compound is prepared from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.75 g, 1.52 mmol), 2N solution of ethylamine in MeOH (3.805 mL, 7.61 mmol) and $NaBH_4$ (0.115 g, 3.04 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4, then CH_2Cl_2/MeOH (10% NH_3 conc.) gradient from 9:1 to 8:2) to give a colorless oil. MS: 522.4 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.47 min.

The corresponding enantiomer **N-((3S,4R)-4-Ethylaminomethyl-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide** is obtained as follows: A solution of (3S,4R)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.27 g, 2.58 mmol) and gaseous ethylamine (0.704 g, 15.5 mmol; Fluka 02940) in 1,2-dichloroethane (10 mL) is stirred at room temperature for 30 min, then sodium triacetoxyborohydride (1.37 g, 6.45 mmol) is added in one portion and the mixture is stirred overnight. The organic phase is washed with saturated aqueous $NaHCO_3$ solution, the water layers are re-extracted with CH_2Cl_2, and the combined organics are dried (Na_2SO_4) and evaporated to dryness to give the title compound. MS: 522.2 $[M+H]^+$.

N-((3S*,4S*)-4-Cyclobutylaminomethyl-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide: from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.00 g, 2.03 mmol), cyclobutylamine (0.74 g, 10.2 mmol) and $NaBH_4$ (0.154 g, 4.06 mmol) to give the title compound as oil. TLC, R_f (hexane/AcOEt) = 0.31. MS: 548.3 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.28 min.

N-Isopropyl-N-[(3S*,4S*)-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-4-methoxy-3-(3-methoxy-propoxy)-benzamide: from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.75 g, 1.52 mmol), isopropylamine (0.654 mL, 7.61 mmol) and $NaBH_4$ (0.115 g, 3.04 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4, then CH_2Cl_2/MeOH (10% NH_3 conc.) gradient from 9:1 to 8:2) to give the title compound as colorless oil. MS: 536.4 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.58 min.

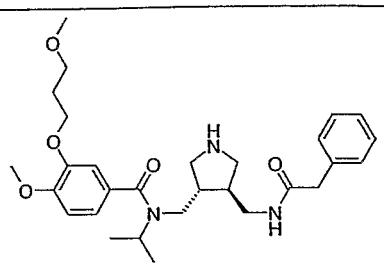
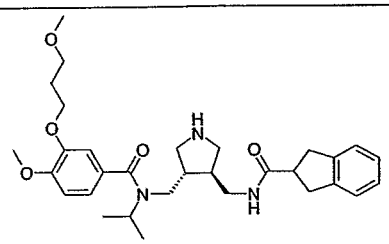
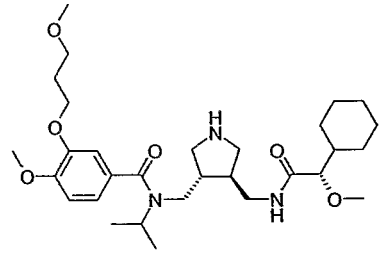
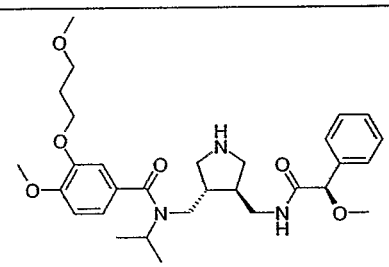
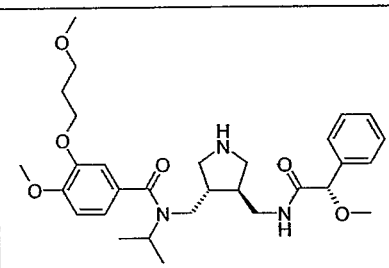
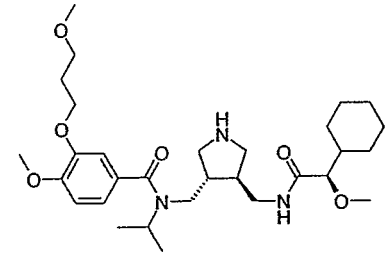
N-[(3S*,4R*)-4-(Isobutylamino-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide: from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.75 g, 1.52 mmol), isobutylamine (0.756 mL, 7.61 mmol) and $NaBH_4$ (0.115 g, 3.04 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4, then CH_2Cl_2/MeOH (10% NH_3 conc.) gradient from 9:1 to 8:2) to give the title compound as colorless oil. MS: 550.4 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.74 min.

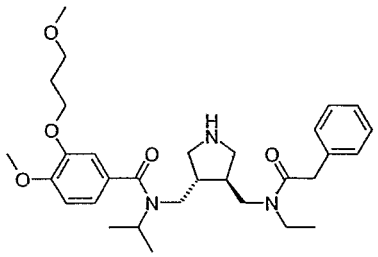
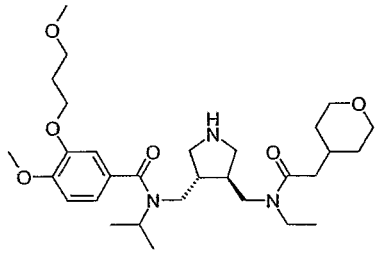
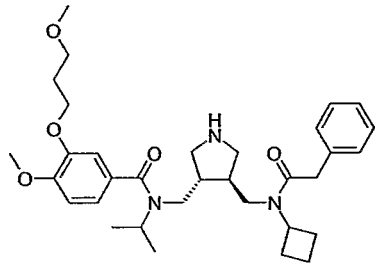
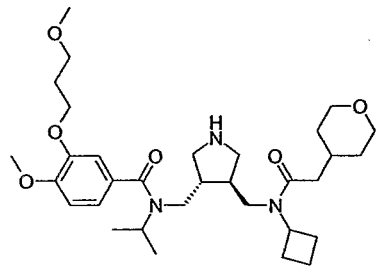
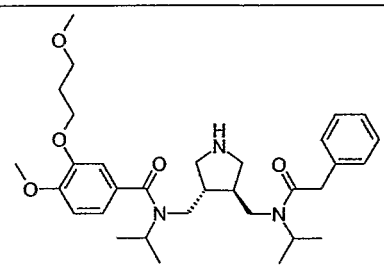
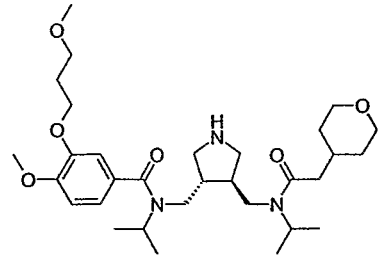
N-{(3S*,4R*)-4-[(Cyclopropylmethyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide: from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.75 g, 1.52 mmol), cyclopropanemethylamine (0.652 mL, 7.61 mmol) and $NaBH_4$ (0.115 g, 3.04 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4, then CH_2Cl_2/MeOH (10% NH_3 conc.) gradient from 9:1 to 8:2) to give the title compound as colorless oil. MS: 548.4 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.66 min.

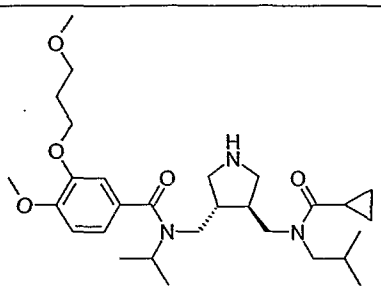
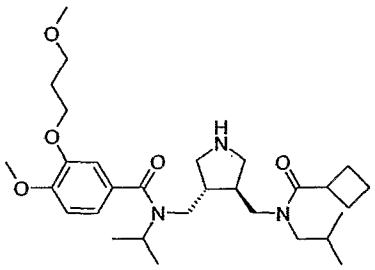
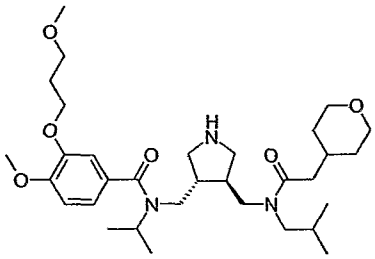
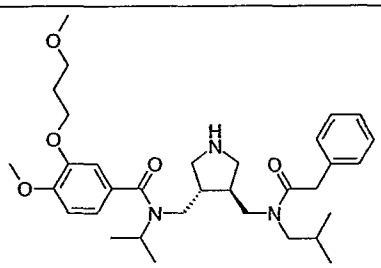
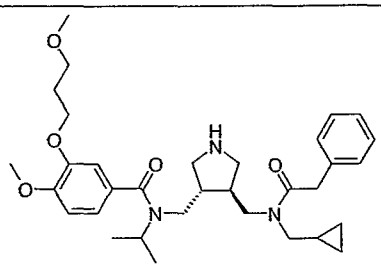
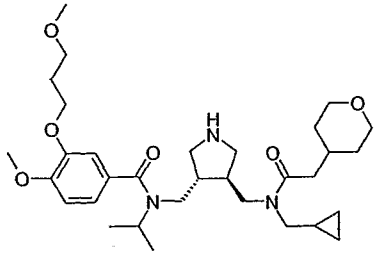
The title compounds in Table 3 are prepared accordingly from the starting materials described above:

Table 3

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)

131	(3S,4S)		512.2	3.47[b]
132	(3S,4S)		538.2	3.83[b]
133	(3S,4S)		548.2	4.00[b]
134	(3S,4S)		542.2	3.59[b]
135	(3S,4S)		542.2	3.57[b]
136	(3S,4S)		548.2	3.98[b]

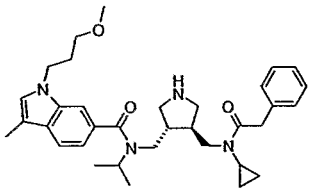
137	(3S,4S)		540.2	3.86[b]
138	(3S,4S)		548.3	4.11[a]
139	(3S*, 4S*)		566.2	4.32[b]
140	(3S*, 4S*)		574.2	3.74[b]
141	(3S*, 4S*)		554.4	4.58[a]
142	(3S*, 4S*)		562.4	4.14[a]

143	(3S*, 4S*)		532.4	4.88[a]
144	(3S*, 4S*)		518.4	4.64[a]
145	(3S*, 4S*)		576.4	4.33[a]
146	(3S*, 4S*)		568.4	4.76[a]
147	(3S*, 4S*)		566.4	4.66[a]
148	(3S*, 4S*)		574.4	4.23[a]

[a] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[b] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

Example 149: 1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid {(3S,4S)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-isopropyl-amide



To a solution of (3R,4R)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.26 g, 0.395 mmol) in dioxane (1 mL), 4N HCl in dioxane (1 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 559 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.35 min.

The starting material is prepared as follows:

A. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (8.5 g, 22 mmol), 1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid (7.6 g, 30.8 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (7.84 g, 30.8 mmol) and triethylamine (12.3 mL, 88 mmol) in CH_2Cl_2 (425 mL) is refluxed overnight under a nitrogen atmosphere and then quenched by the addition of an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous phase is extracted 3 times with AcOEt. The combined organic extracts are concentrated *in vacuo*. The residual oil is taken up in a mixture of THF and MeOH, NaOH 1N is added to cleave the

anhydride side product and the mixture stirred for 3 h. The solvents are concentrated, CH_2Cl_2 is added and the layers are separated. The aqueous one is then back extracted twice with CH_2Cl_2 and the combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is used in the next step without further purification. TLC, R_f (AcOEt) = 0.6. MS (LC-MS): 516.3 $[M\text{-}Boc+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 8.60 min.

B. (3S,4R)-3-Hydroxymethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (13.8 g, 22 mmol) in MeCN (350 mL) is added tetraethylammonium fluoride hydrate (6.6 g, 44 mmol) under a nitrogen atmosphere. The reaction mixture is refluxed for 3 h. Water and AcOEt are added, the layers are separated and the aqueous one extracted twice with AcOEt. The combined organic extracts are dried (Na_2SO_4), filtered and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 90:10) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.2. MS (LC-MS): 402.2 [M+H-Boc]+; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.85 min.

C. (3S,4R)-3-Formyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound under I in Scheme 5 from (3S,4R)-3-hydroxymethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.6. t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.11 min.

D. (3R,4R)-3-Cyclopropylaminomethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

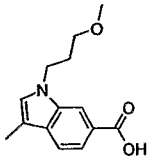
To a solution of (3S,4R)-3-formyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (6 g, 10.9 mmol) in

dichloroethane (100 mL), cyclopropylamine (0.85 mL, 12 mmol) and $NaBH(OAc)_3$ (4.32 g, 15.3 mmol) are added. The solution is stirred at RT overnight, then diluted with CH_2Cl_2. A saturated solution of $NaHCO_3$ is added, the layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material is purified by flash chromatography on silica gel (eluent: AcOEt/MeOH 100:0 to 85:15) to give the title compound. TLC, R_f (AcOEt) = 0.1. MS (LC-MS): 541.3 [M+H]+; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.52 min.

E. (3R,4R)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound under K in Example 9 (Scheme 5) from (3R,4R)-3-cyclopropylaminomethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester. MS (LC-MS): 658.9 $[M\text{-}Boc+H]^+$. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.69 min.

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid



3-Methyl-1H-indole-6-carboxylic acid methyl ester

A mixture of 3-formyl-1H-indole-6-carboxylic acid methyl ester (5 g, 24.6 mmol), p-toluene-sulfonic acid (704 mg, 3.7 mmol) and p-toluenesulfonylhydrazide (5.49 g, 29.5 mmol) in a mixture of dimethylformamide (50 mL) and sulfolane (25 mL) is heated at 100°C for 15 min. Then cooled to RT, before the addition of sodium cyanoborohydride (6.2 g, 98.4 mmol, 2 g portions after 10 min intervals). The resulting mixture is heated at 100°C for 2 h, cooled to RT and poured into a mixture of ice and water (250 mL) leading to a white precipitate. Water (500 mL) is added, and the mixture is stirred for 30 min before filtration. The off-white solid is washed with warm water. Toluene is added and removed by rotary evaporation to afford the

title compound as a yellow solid. TLC, R_f (hexane/AcOEt 4:1)= 0.3. MS (LC-MS): [M+H]+= 188.1. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.13 min.

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid methyl ester

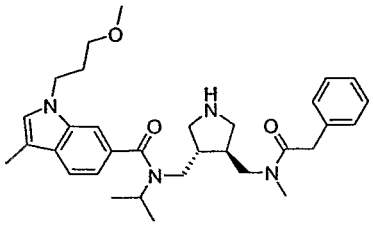
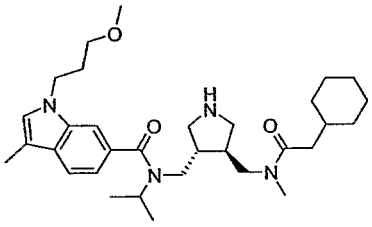
To a solution of 3-methyl-1H-indole-6-carboxylic acid methyl ester (2.5 g, 13.2 mmol) in DMF (25 mL), a solution of NaH (580 mg, 14.5 mmol, 60% dispension in grease) in DMF (25 mL) is slowly added under a N_2 atmosphere. The mixture is stirred at 80°C for 20 min, and cooled to RT before the addition of 1-bromo-3-methoxypropane (4.04 g, 26.4 mmol). The resulting mixture is stirred for 24 h. 1-Bromo-3-methoxypropane (2.02 g, 13.2 mmol) and NaH (580 mg, 14.5 mmol) are added and the mixture further stirred for 24 h to complete the reaction. The solvent is concentrated under reduced pressure and the mixture diluted with AcOEt. An aqueous saturated solution of $NaHCO_3$ is added, the layers are separated, and the aqueous one is back-extracted with AcOEt. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude residue is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 80:20) to give the title compound. MS (LC-MS): 262.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.80 min.

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid

To a solution of 1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid methyl ester (1.56 g, 6.3 mmol) in MeOH (20 mL) and H_2O (1 mL) is added NaOH (756 mg, 18.9 mmol) and the mixture is stirred at 50°C overnight. Then neutralized by the addition of water and HCl 1.0 M (3 eq, 18.9 mmol). CH_2Cl_2 is added, the layers are separated, and the aqueous one is extracted twice with CH_2Cl_2. The combined organic layers are dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material is obtained in a pure form and is used in the next step without purification. MS (LC-MS): 248.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.93 min.

The following Examples are prepared according to the procedures described above for Example 149 :

Table 4

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
150	(3S, 4S)		533	5.20[a]
151	(3S, 4S)		539	5.64[a]

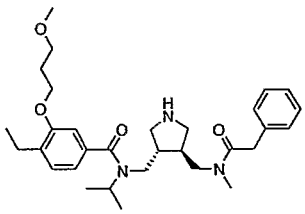
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

The starting materials of the title compounds in Table 4 are prepared as follows:

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid {(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-isopropyl-amide

In a similar manner as described in Example 9 for the reaction step J, the following starting material is prepared from (3S,4R)-3-formyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared under C in example 151) (3 g, 5.4 mmol), 2N solution of methylamine in MeOH (13.5 mL, 27 mmol) and $NaBH_4$ (0.408 g, 10.8 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 90:10, then AcOEt/MeOH/NH_4OH 89:10:1) to give a colorless oil. MS: 515.0 $[M+H]^+$. $]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.41 min.

Example 152 : 4-Ethyl-N-isopropyl-3-(3-methoxy-propoxy)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide



To a solution of (3R,4R)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (0.330 g, 0.529 mmol) in dioxane (2 mL), 4N HCl in dioxane (2 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 524.3 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.94 min.

The starting material is prepared in a similar manner as described in Example 149, reaction steps A to E, as follows:

A. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (8.5 g, 22 mmol), 4-ethyl-3-(3-methoxy-propoxy)-benzoic acid (5.76 g, 24.2 mmol), BOPCl (6.16 g, 24.2 mmol) and triethylamine (12.3 g, 88 mmol). TLC, Rf (CH_2Cl_2/MeOH 95:5) = 0.32. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 8.81 min. MS (LC-MS): [M+H-BOC]+ 507.3

B. (3R,4S)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (13.1 g, 21.6 mmol) and TBAF (17 g, 54 mmol), and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5) to give the title compound as yellow oil. TLC, Rf (AcOEt) = 0.4,MS (LC-MS): 437.3 $[M+H-tBu]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH3CN/H2O/5 min, 100% CH_3CN/3 min, CH_3CN and H2O containing 0.1% TFA, flow: 1.5 mL/min) : 6.74 min.

C. (3R,4S)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4S)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (8.8 g, 17.9 mmol) and Dess Martin Periodinane (7.6 g, 17.9 mmol) to give the title product as a yellow oil which was used in the next step without purification. TLC, Rf (AcOEt) = 0.55. t_R (tR (HPLC, Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH3CN/H2O/3.5 min, 95% CH3CN/2 min, CH3CN and H2O containing 0.1% HCOOH, flow: 0.6 mL/min): 3.77 min.

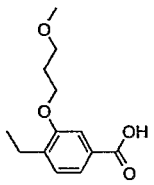
D. (3R,4R)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

In a similar manner as described in Example 9 for the reaction step J, the following starting materials is prepared from (3R,4S)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (3.5 g, 6 mmol), methyl amine (0.93 mL, 30 mmol) and $NaBH_4$ (0.454 g, 12 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 1:1) to (CH_2Cl_2/MeOH/NH_4OH 89:10:1) to give the title compound as colorless oil. TLC, Rf (CH2Cl2/MeOH/NH4OH 89:10:1) = 0.29. MS (LC-MS): 506.2 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min) : 5.38 min.

E. (3R,4R)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4R)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (0.7 g, 1.38 mmol), phenylacetyl chloride (0.22 mL, 1.66 mmol) and triethylamine (0.21 mL, 2.1 mmol) in CH_2Cl_2 (40 mL) and purification by flash chromatography on silica gel (c-hexane/AcOEt 1:1 to 0:1) to give the title compound as colorless oil. TLC, Rf (AcOEt) = 0.30. MS (LC-MS): 624.0 $[M+H]^+$; t_R (Waters Symmetry C18 column, 20-100% CH_3CN/H_2O/5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min) : 4.41 min.

4-Ethyl-3-(3-methoxy-propoxy)-benzoic acid



a. 4-Bromo-3-hydroxy-benzoic acid methyl ester

To a solution of 4-bromo-3-hydroxy-benzoic acid (prepared according to J. Amer. Chem Soc. 1946, 68, 574) (5 g, 32.8 mmol) in MeOH (100 mL), conc. H_2SO_4 (1 mL) is added. The solution is refluxed for 14 h, then concentrated to about 30 mL and poured into a water. The aqueous layer is extracted with ether (50 mL x 4) and the combined organic extracts are neutralized with a saturated aqueous solution of $NaHCO_3$ (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound as a white powder. TLC, R_f (AcOEt) = 0.9. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 5.8 (bs, 1H), 7.45 (d, 1H), 7.55 (d, 1H), 7.7 (s, 1H) ppm.

b. 4-Bromo-3-(3-methoxy-propoxy)-benzoic acid methyl ester

A solution of 4-bromo-3-hydroxy-benzoic acid methyl ester (12 g, 51.9 mmol), potassium carbonate (10.77 g, 77.9 mmol) and 1-iodo-3-methoxy propane (11.42 g, 57.1 mmol) in acetonitrile (250 mL) is stirred at reflux for 16 h. The solvent is concentrated under reduced pressure, H_2O (100 mL) is added, and the aqueous layer extracted with ether (50 mL x 4). The combined organic extracts are washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the title which was used without further purification in the next step. TLC, R_f (hexane/AcOEt 2:1) = 0.65. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.12 (p, 2H), 3.38 (s, 3H), 3.63 (t, 2H), 3.9 (s, 3H), 4.2 (t, 2H), 7.5 (d, 1H), 7.55 (m, 1H), 7.6 (d, 1H) ppm.

c. 3-(3-Methoxy-propoxy)-4-trimethylsilanylethynyl-benzoic acid methyl ester

To a stirred solution of 4-bromo-3-(3-methoxy-propoxy)-benzoic acid methyl ester (5 g, 16.49 mmol) and trimethylsilyl actetylene (2.74 mL, 19.8 mmol) in triethylamine (60 mL), $Cl_2Pd(PPh_3)_2$ (2.31 g, 3.29 mmol) and CuI (0.314 g, 1.65 mmol) are added. The resulting mixture is stirred at RT for 15 h and concentrated under reduced pressure. The crude residue is purified by flash chromatography on silica gel (eluent: hexane/AcOEt 10:1 to 5:1) to give the desired title product as a brown oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 0.25 (s, 9H), 2.12 (p, 2H), 3.38 (s, 3H), 3.65 (t, 2H), 3.9 (s, 3H), 4.18 (t, 2H), 7.45 (d, 1H), 7.52 (s, 1H), 7.58 (d, 1H) ppm.

d. 4-Ethynyl-3-(3-methoxy-propoxy)-benzoic acid

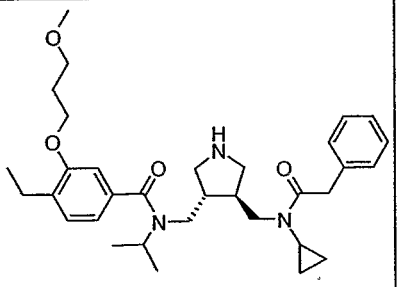
To a solution of 3-(3-methoxy-propoxy)-4-trimethylsilanylethynyl-benzoic acid methyl ester (16.49 mmol) in MeOH (40 mL) is added KOH (1 N, 24.7 mL, 24.7 mmol). The resulting mixture is stirred at RT for 15 h and concentrated under reduced pressure. The residue was taken up in HCl (2 N, 100 mL) and extracted with AcOEt (100 mL x 3). The combined organic extracts are washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the title as a yellow oil which is used without further purification in the next step. MS (FAB): 235.0 $[M+H]^+$.^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.15 (p, 2H), 3.38 (s, 3H), 3.41 (s, 1H), 3.62 (t, 2H), 4.22 (t, 2H), 7.5 (d, 1H), 7.65 (s, 1H), 7.68 (d, 1H) ppm.

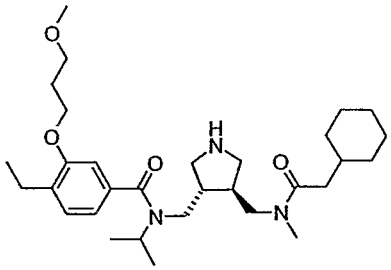
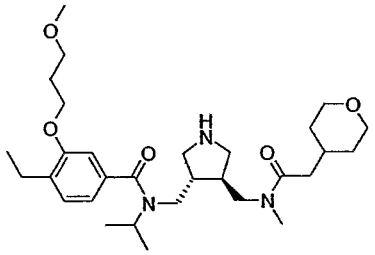
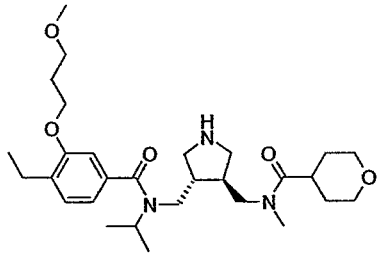
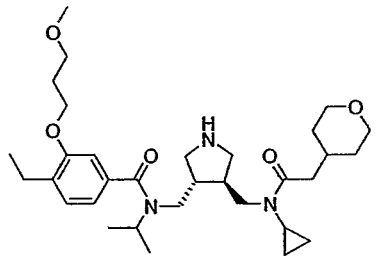
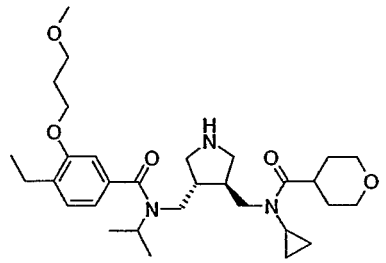
e. 4-Ethyl-3-(3-methoxy-propoxy)-benzoic acid

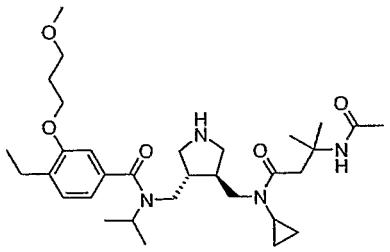
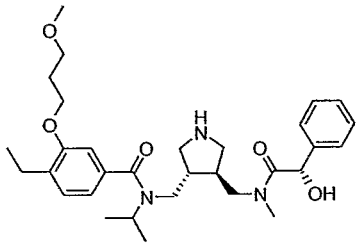
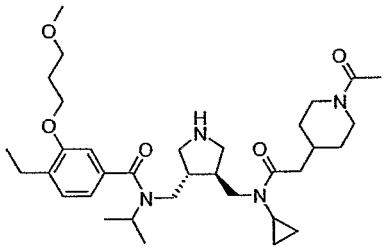
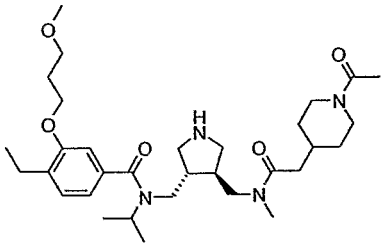
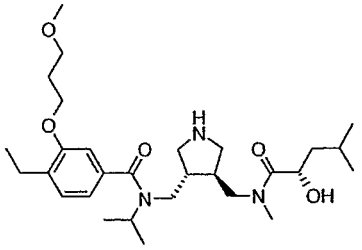
To a solution of 4-ethynyl-3-(3-methoxy-propoxy)-benzoic acid (1 g, 4.11 mmol) in EtOH (20 mL), $Pd(OH)_2$ (0.1 g) is added. The resulting mixture is stirred under an hydrogen atmosphere for 15 min, then filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: hexane/AcOEt 2:1) to give the title compound as white powder. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.2 (t, 3H), 2.15 (p, 2H), 2.7 (q, 2H), 3.38 (s, 3H), 3.62 (t, 2H), 4.15 (t, 2H), 7.25 (d, 1H), 7.55 (s, 1H), 7.68 (d, 1H) ppm.

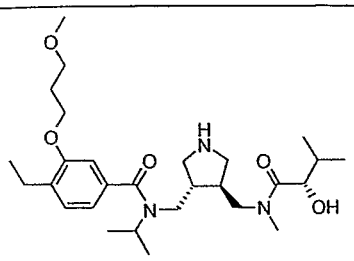
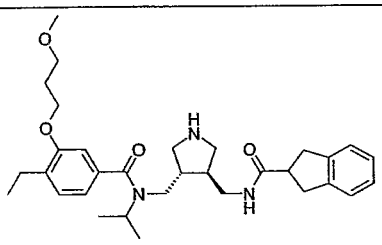
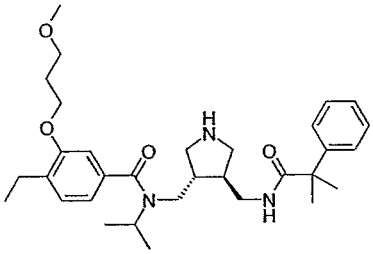
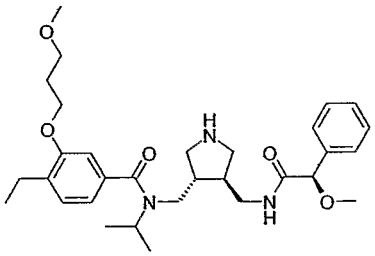
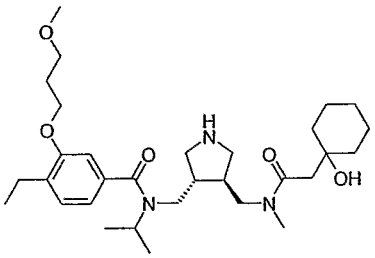
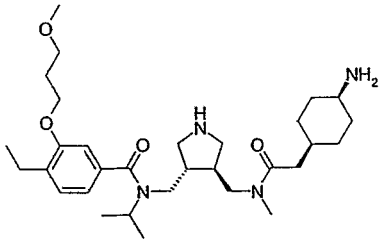
The following Examples are prepared according to the procedures described above for Example 152 :

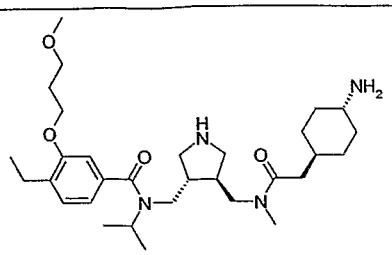
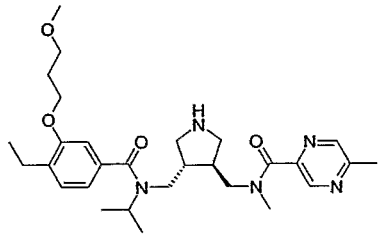
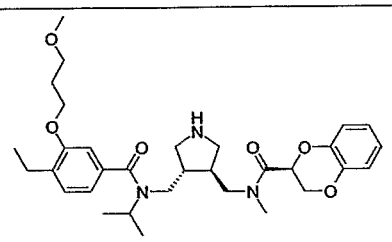
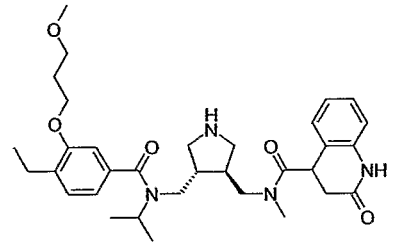
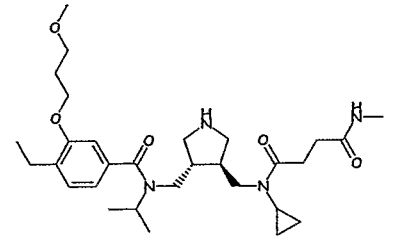
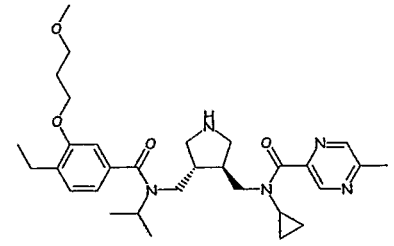
Table 5

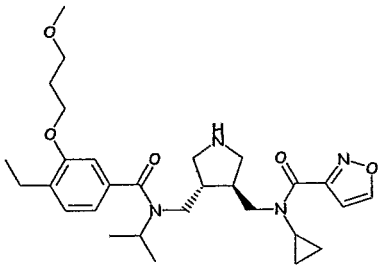
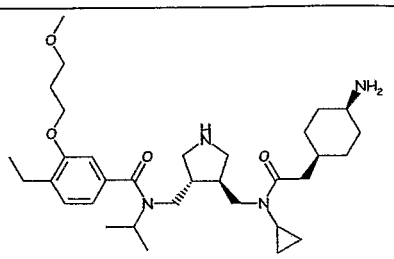
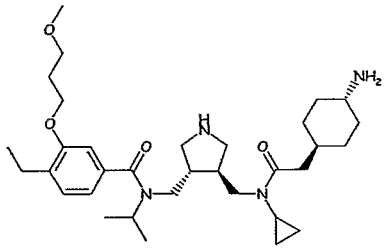
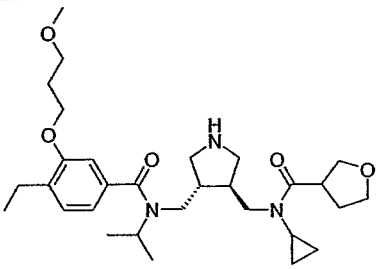
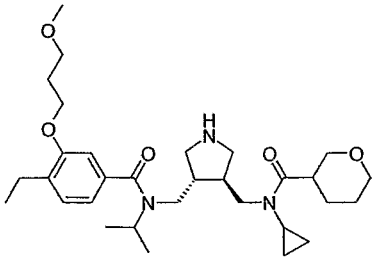
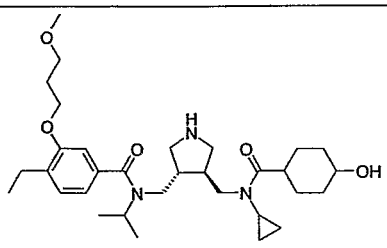
Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
153	(3S, 4S)		550.2	6.13[a]

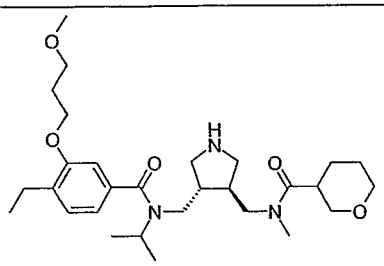
154	(3S, 4S)		530	5.55[a]
155	(3S, 4S)		532	4.10[b]
156	(3S, 4S)		518	3.97[b]
157	(3S, 4S)		558.3	4.37[b]
158	(3S, 4S)		544.3	4.25[b]

159	(3S, 4S)		573.3	2.63[c]
160	(3S, 4S)		540.3	4.88[a]
161	(3S, 4S)		599.2	2.60[c]
162	(3S, 4S)		573.2	2.20[c]
163	(3S, 4S)		520.3	2.94[d]

164	(3S, 4S)		506.4	2.86 min[d]
165	(3S,4S)		536.2	4.71[f]
166	(3S,4S)		538.2	4.76[f]
167	(3S,4S)		540.2	4.47[f]
168	(3S,4S)		546.2	4.52[f]
169	(3S,4S)		545.5	4.26[e]

170	(3S,4S)		545.5	4.25[e]
171	(3S,4S)		526.3	4.69[e]
172	(3S,4S)		568.2	5.24[e]
173 174	(3S,4S)		579.3 579.3	4.78[e] 4.67[e]
175	(3S,4S)		545.3	4.62[e]
176	(3S,4S)		552.3	4.86[e]

177	(3S,4S)		527.2	4.89[e]
178	(3S,4S)		571.4	4.35[e]
1791	(3S,4S)		571.4	4.41[e]
180 181	(3S,4S)		530.2	4.16[f] 4.16[f]
182 183	(3S,4S)		544.2	4.28[f] 4.32[f]
184 185	(3S,4S)		558.3	3.98[f] 4.20[f]

186 187	(3S,4S)		518.2	4.00[f] 4.04[f]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (HPLC, Nucleosil C-18HD (4x70mm, 3µm), 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/ 1.5 min; flow: 1 mL/min).

[c] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[d] t_R (Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[e] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[f] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

The starting materials of the title compounds in Table 5 are prepared as follows:

(3R,4R)-3-Aminomethyl-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

According to the procedure described for Example 130 / reaction step C, by hydrogenation of (3S,4R)-3-azidomethyl-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (3.95 g, 7.48 mmol), dissolved in absolute EtOH (100 mL), in the presence of Pd/C 10% (0.8 g; Engelhard 4505) at room temperature under atmospheric pressure to give, after filtration and drying in vacuo, the title compound as colorless oil. MS: 492.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.62 min.

a. (3R,4S)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: prepared from

(3R,4S)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (4.00 g, 8.12 mmol), methane sulfonylchloride (0.733 mL, 9.34 mmol) and NEt_3 (3.40 mL, 24.4 mmol) in CH_2Cl_2 (50 mL) similar to the procedure described for Example 130 / reaction step A, to give the title compound as yellowish oil. TLC, R_f (hexane/AcOEt 1:3) = 0.32.

b. (3S,4R)-3-Azidomethyl-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester: prepared from (3R,4S)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (5.50 g, 8.10 mmol) and NaN_3 (2.13 g, 32.4 mmol) in DMF (40 mL) similar to the procedure described for Example 130 / reaction step B, and purification by flash chromatography on silica gel (hexane/AcOEt 1:1) to give the title compound as colorless oil. TLC, R_f (hexane/AcOEt 1:3) = 0.47. MS: 518.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.89 min.

(3R,4R)-3-Cyclopropylaminomethyl-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

To a solution of (3R,4S)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (described under step C in example 152) (6.9 g, 11.88 mmol) in dichloroethane (112 mL), cyclopropylamine (0.92 mL, 13.1 mmol) and $NaBH(OAc)_3$ (3.52 g, 16.63 mmol) are added. The solution is stirred at RT overnight, then diluted with CH_2Cl_2. A saturated solution of $NaHCO_3$ is added, the layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material is purified by flash chromatography on silica gel (eluent: AcOEt/MeOH 100:0 to 85:15) to give the title compound. MS (LC-MS): 532.3 [M+H]+; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.58 min.

The starting materials of Examples 173 and 174 are prepared as follows:

The two diastereomers (3R,4R)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4(R)-{[methyl-(2-oxo-1,2,3,4-tetrahydro-quinoline-4-carbonyl)-amino]-

methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4(S)-{[methyl-(2-oxo-1,2,3,4-tetrahydro-quinoline-4-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.5 g) on a Chiralcel OD column (20 mM; 5x50 cm) using n-hexane/EtOH/MeOH 90:7.5:2.5 as eluent (flow 90 mL/min, UV detection 210 nm).

The starting materials of Examples 180 and 181 are prepared as follows:

The two diastereomers (3R,4R)-3-{[cyclopropyl-(tetrahydro-furan-3(R)-carbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(tetrahydro-furan-3(S)-carbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.33 g) on a Chiralpak AD column (20 µM; 50x500 mm) using n-hexane/EtOH/MeOH 80:17.5:2.5 (flow rate: 110 mL/min, UV 210 nm).

The starting materials of Examples 182 and 183 are prepared as follows:

The two diastereomers (3R,4R)-3-{[cyclopropyl-(tetrahydro-pyran-3(R)-carbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(tetrahydro-pyran-3-carbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.33 g) on a Chiralpak OD column (20 µM; 50x500 mm) using n-hexane/EtOH/MeOH 97:1.5:1.5 (flow rate: 120 mL/min, UV 210 nm).

The starting materials of Examples 184 and 185 are prepared as follows:

The two diastereomers (3R,4R)-3-{[cyclopropyl-cis-(4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-

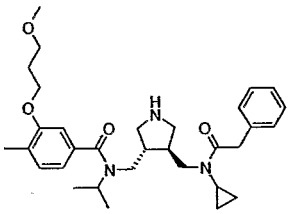
pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-trans-(4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of

the diastereoisomeric mixture (0.32 g) on a Chiralpak OD column (20 µM; 5x50 cm) using n-hexane/EtOH/MeOH 97:1.5:1.5 as eluent (flow 120 mL/min, UV detection 210 nm).

The starting materials of Examples 186 and 187 are prepared as follows:

The two diastereomers (3R,4R)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-{[methyl-(tetrahydro-pyran-3(R)-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-{[methyl-(tetrahydro-pyran-3(S)-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.28 g) on a Chiralcel AD-H column (30x250 cm) using a gradient 2-propanol/CO_2 (flow 130 mL/min, UV detection 220 nm).

Example 188 : N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide



To a solution of (3R,4R)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.280 g, 0.44 mmol) in dioxane (3 mL), 4N HCl in dioxane (2.5 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 536.2 $[M+H]^+$; t_R (HPLC, Nucleosil C-18HD (4x70mm, 3µm), 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/ 1.5 min; flow: 1 mL/min): 4.56 min.

The starting material is prepared in a similar manner as described in Example 149, reaction steps A to E, as follows:

A. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (5 g, 12.9 mmol), 4-methyl-3-(3-methoxy-propoxy)-benzoic acid (4.06 g, 18.1 mmol), BOPCl (4.6 g, 18.1 mmol) and triethylamine (7.2 mL, 51.7 mmol). TLC, Rf (AcOEt) = 0.7. MS (LC-MS): 493 $[M+H-Boc]^+$.

B. (3R,4S)-3-({[4-Methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (6.79 g, 11.5 mmol) and TBAF (5.42 g, 17.2 mmol) to give the title compound as yellow oil which was used in the next step without purification. TLC, Rf (AcOEt) = 0.4. MS (LC-MS): 423 $[M+H-tBu]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH3CN/H2O/5 min, 100% CH_3CN/3 min, CH_3CN and H2O containing 0.1% TFA, flow: 1.5 mL/min) : 6.05 min.

C. (3R,4S)-3-({[4-Methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4S)-3-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (5.7 g, 11.9 mmol) and Dess Martin Periodinane (5.1 g, 11.9 mmol) to give the title product as a yellow oil which was used in the next step without purification. TLC, Rf (AcOEt) = 0.49.

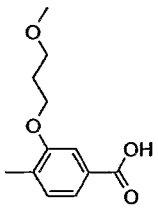
D. (3R,4R)-3-({[4-Methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-cyclopropylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4S)-3-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (3 g, 6.29 mmol), cyclopropyl amine (0.395 mL, 6.92 mmol) and $NaBHOAc_3$ (1.87 g, 8.81 mmol) and purification by flash chromatography on silica gel (AcOEt/MeOH 100:0 to 85:15) to give the title compound as colorless oil. TLC, Rf (AcOEt) = 0.63. MS (LC-MS): 518.3 $[M+H]^+$; t_R (HPLC, Nucleosil C-18HD (4x70mm, 3µm), 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/ 1.5 min; flow: 1 mL/min): 5.37 min.

E. (3R,4R)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4R)-3-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-cyclopropylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (0.3 g, 0.579 mmol), phenylacethyl chloride (0.092 mL, 0.695 mmol) and triethylamine (0.12 mL, 0.869 mmol) and purification by flash chromatography (c-hexane/AcOEt 1:1 to 0:1) to give the title compound as colorless oil. TLC, R_f (AcOEt/c-hexane 4:1) = 0.15. MS (LC-MS): 610.3 $[M+H]^+$; (LC-MS Waters Symmetry C18, 2.1x30mm, 20-100% CH_3CN/5 min) : 4.63 min.

3-(3-Methoxy-propoxy)-4-methyl-benzoic acid



a. 3-Hydroxy-4-methyl-benzoic acid methyl ester

To a solution of 3-hydroxy-4-methyl-benzoic acid (5 g, 32.8 mmol) in MeOH (100 mL) cc H_2SO_4 (1 mL) is added. The solution is refluxed for 14 h, then concentrated to about 30 mL and poured into water. The aqueous layer is extracted with ether (50 mL x 4) and the combined organic extracts are neutralized with a saturated aqueous solution of $NaHCO_3$ (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound as a white powder. TLC, R_f (hexane/AcOEt 2:1) = 0.55. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.3 (s, 3H), 3.9 (s, 3H), 7.15 (d, 1H), 7. 5 (d, 1H), 7.6 (s, 1H) ppm.

b. 3-(3-Methoxy-propoxy)-4-methyl-benzoic acid methyl ester

A solution of 3-hydroxy-4-methyl-benzoic acid methyl ester (7.7 g, 32.43 mmol), potassium carbonate (6.72 g, 48.65 mmol) and 1-iodo-3-methoxy propane (7.14 g, 35.68 mmol) in acetonitrile (125 mL) is stirred at reflux for 26 h. The solvent is concentrated under reduced pressure, H_2O (100 mL) is added, and the aqueous layer is extracted with ether (50 mL x 4). The combined organic extracts are washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the title which is used without further purification in the next step. TLC, R_f (hexane/AcOEt 2:1) = 0.65. ^{1}H-NMR ($CDCl_3$, 300 MHz):

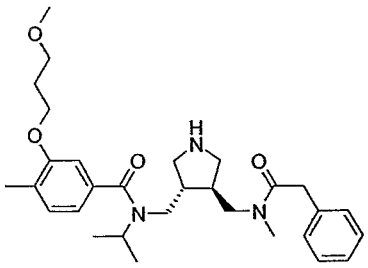
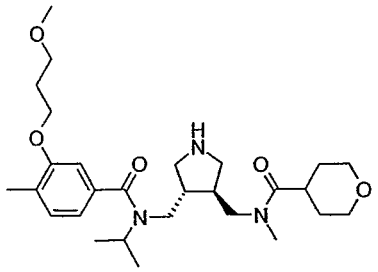
δ = 2.10 (p, 2H), 2.3 (s, 3H), 3.38 (s, 3H), 3.62 (t, 2H), 3.9 (s, 3H), 4.15 (t, 2H), 7.15 (d, 1H), 7.45 (s, 1H), 7.55 (d, 1H) ppm.

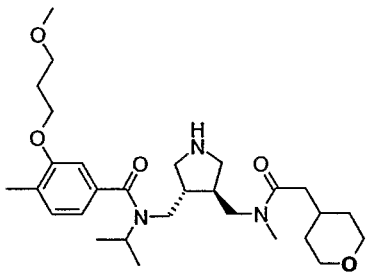
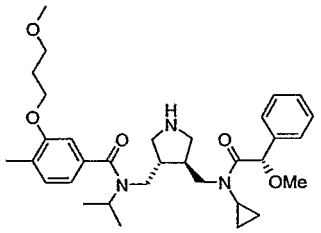
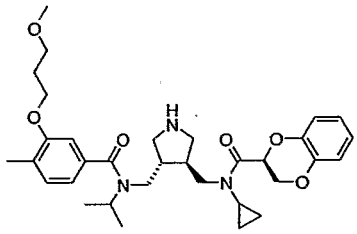
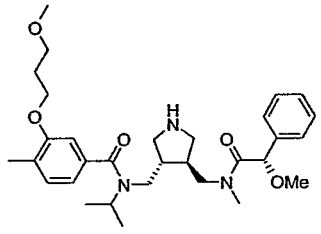
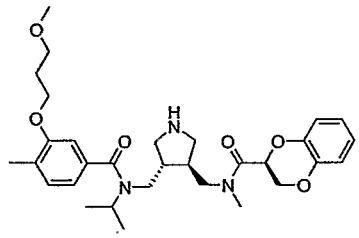
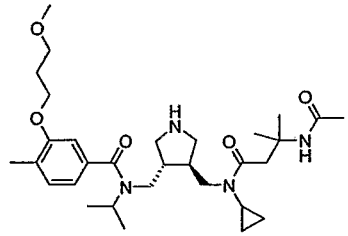
c. 3-(3-Methoxy-propoxy)-4-methyl-benzoic acid

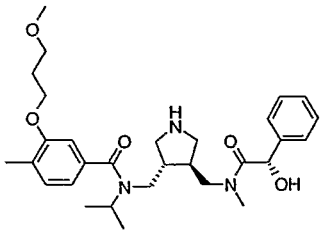
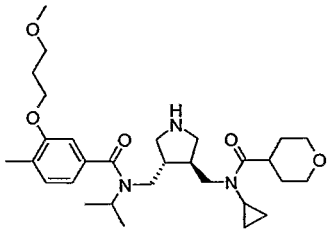
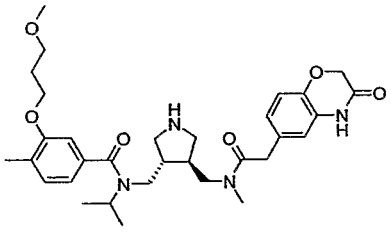
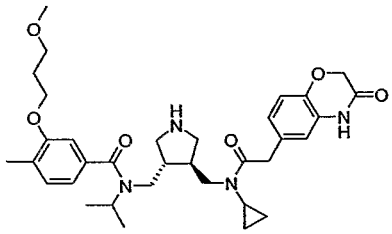
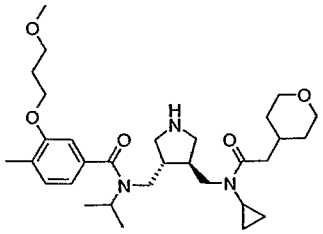
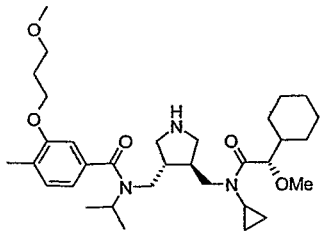
A solution of 3-(3-methoxy-propoxy)-4-methyl-benzoic acid methyl ester (7.12 g, 32.86 mmol) and NaOH (1 N in water, 100 mL, 100 mmol) in EtOH (100 mL) is refluxed for 1 h. The reaction mixture is allowed to reach RT, and the solvent is concentrated under reduced pressure. The residue is dissolved in water (200 mL) and washed with ether (50 mL x 3). The pH is adjusted to 2 by addition of cc HCl and the aqueous layer extracted with AcOEt (150 mL x 2). The combined organic extracts are dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material is recrystallized in diethyl ether/hexane to afford the desired title product. TLC, R_f (hexane/AcOEt 2:1) = 0.15. MS (LC-MS): 224.0 $[M-H]^+$. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.10 (p, 2H), 2.3 (s, 3H), 3.38 (s, 3H), 3.62 (t, 2H), 4.15 (t, 2H), 7.2 (d, 1H), 7.55 (s, 1H), 7.65 (d, 1H) ppm.

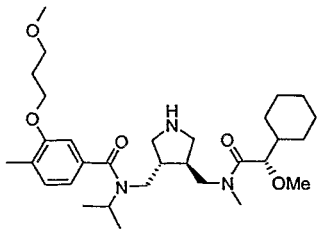
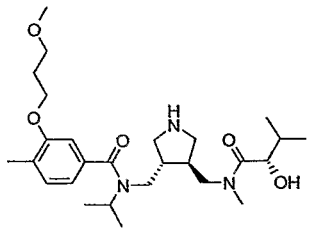
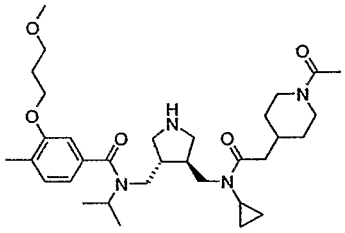
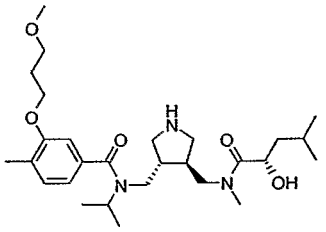
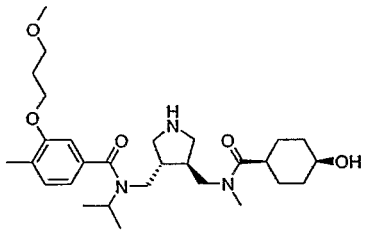
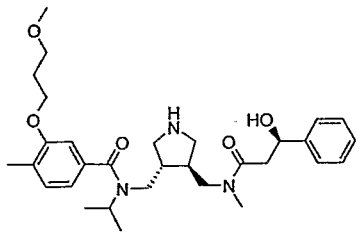
The following Examples are prepared according to the procedures described above for Example 188 :

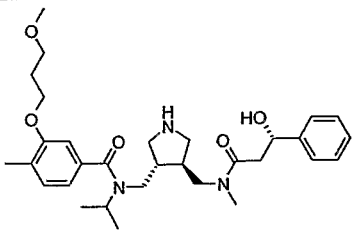
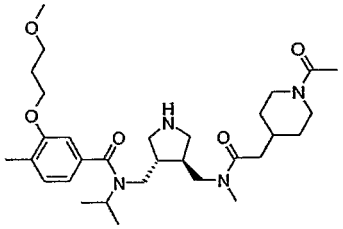
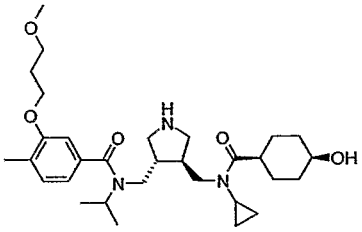
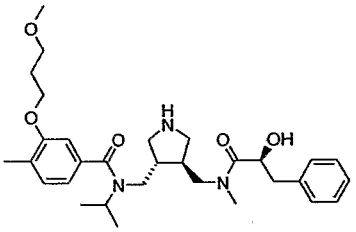
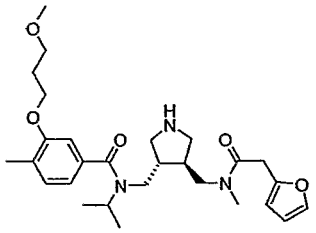
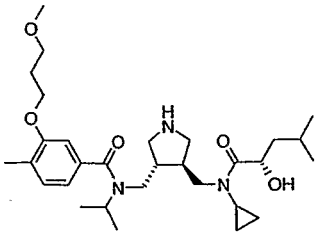
Table 6

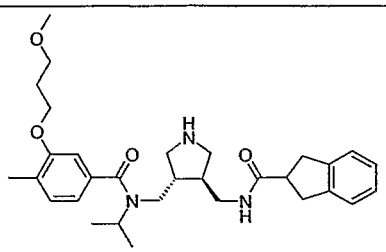
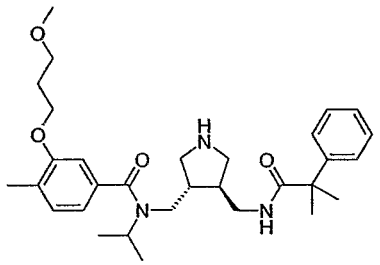
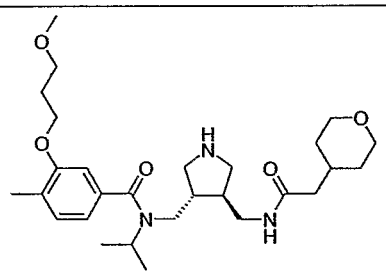
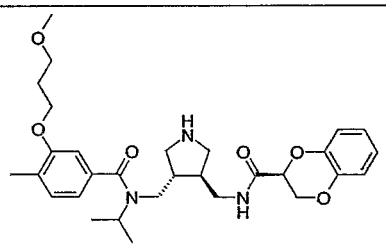
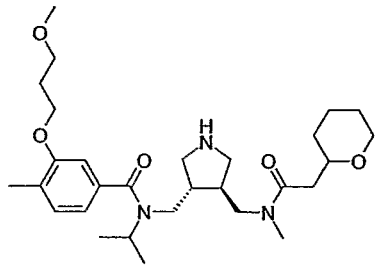
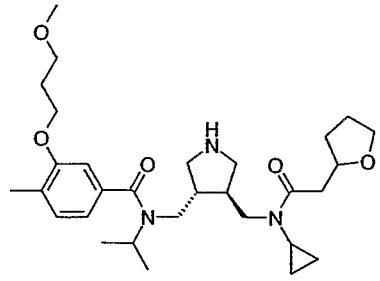
Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
189	(3S, 4S)		510.2	4.21[a]
190	(3S, 4S)		504.4	4.45[a]

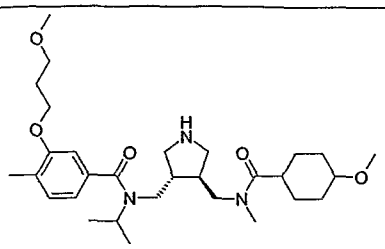
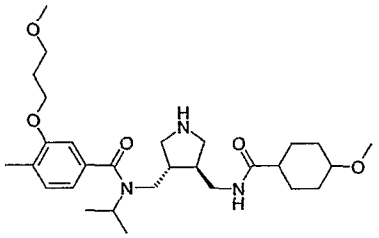
191	(3S, 4S)		518.3	4.47[a]
192	(3S, 4S)		566.2	4.92[a]
193	(3S, 4S)		580.3	5.14[a]
194	(3S, 4S)		540.3	4.81[a]
195	(3S, 4S)		554.2	4.96[a]
196	(3S, 4S)		559.3	4.69[a]

197	(3S, 4S)		526.3	4.71[a]
198	(3S, 4S)		530.3	4.64[a]
199	(3S, 4S)		581.2	2.45[b]
200	(3S, 4S)		607.2	2.60[b]
201	(3S, 4S)		544.2	2.30[b]
202	(3S, 4S)		572.3	3.05[c]

203	(3S, 4S)		546.3	3.02[c]
204	(3S, 4S)		492.3	2.46[b]
205	(3S, 4S)		585.3	2.47[b]
206	(3S, 4S)		506.4	2.82[c]
207	(3S, 4S)		518.3	2.67[c]
208	(3S, 4S)		540.3	2.57[b]

209	(3S, 4S)		540.3	2.61[b]
210	(3S, 4S)		559.2	1.87[b]
211	(3S, 4S)		544.3	2.79[c]
212	(3S, 4S)		540.3	2.66[b]
213	(3S, 4S)		500.2	2.52[b]
214	(3S, 4S)		532.3	2.89[c]

215	(3S,4S)		522.2	4.45[e]
216	(3S,4S)		524.2	4.53[e]
217	(3S,4S)		504.2	3.53[e]
218	(3S,4S)		540.2	4.94[d]
219 220	(3S,4S)		518.3	3.97e 3.99e
221 222	(3S,4S)		530.2	4.07[e] 4.09[e]

223 224	(3S,4S)		532.2	3.92[e] 4.08[e]
225 226	(3S,4S)		518.2	3.76[e] 3.90[e]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[c] t_R (Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[d] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[e] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

The starting materials of the title compounds in Table 6 are prepared as follows:

(3R,4R)-3-Aminomethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

According to the procedure described for Example 130/reaction step C, by hydrogenation of (3S,4R)-3-azidomethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (3.68 g, 7.31 mmol), dissolved in MeOH (80 mL), in the presence of Pd/C 10% (1.0 g; Engelhard 4505) at room temperature under atmospheric pressure to give, after filtration and drying in vacuo, the title compound as oil. MS: 478.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.28 min.

a. (3R,4S)-3-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: prepared from (3S,4R)-3-hydroxymethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (3.80 g, 7.94 mmol), methane sulfonylchloride (0.717 mL, 9.13 mmol) and NEt_3 (3.32 mL, 23.8 mmol) in CH_2Cl_2 (50 mL) similar to the procedure described for Example 130 / reaction step A, to give the title compound as yellowish oil. TLC, R_f (hexane/AcOEt 1:3) = 0.21.

b. (3S,4R)-3-Azidomethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester: prepared from (3R,4S)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-methane-sulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (4.42 g, 7.94 mmol) and NaN_3 (2.09 g, 31.8 mmol) in DMF (40 mL) similar to the procedure described for Example 130 / reaction step B, and purification by flash chromatography on silica gel (hexane/AcOEt 1:1) to give the title compound as oil. TLC, R_f (hexane/AcOEt 1:3) = 0.45. MS: 504.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.65 min.

(3R,4R)-3-({[4-Methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

In a similar manner as described in Example 9 for the reaction step J, the following starting materials is prepared from (3R,4S)-3-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared under C in example 190) (2 g, 4.2 mmol), 2N solution of methylamine in MeOH (10.5 mL, 21 mmol) and $NaBH_4$ (0.318 g, 8.40 mmol) and purification by flash chromatography on silica gel (AcOEt/MeOH 90:10, then AcOEt/MeOH/NH_4OH 89:10:1) to give a colorless oil. MS: 492.1 $[M+H]^+$.

The starting materials of Examples 219 and 220 are prepared as follows:

The two diastereomers (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[methyl-(2-tetrahydro-pyran-2(R)-yl-acetyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[methyl-(2-tetrahydro-pyran-2(S)-yl-acetyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the

diastereoisomeric mixture (0.59 g) on a Chiralpak AD column (20 μM; 5x50 cm) using n-hexane/isopropanol 8:2, containing 0.1% TFA, as eluent (flow 100 mL/min, UV detection 210 nm).

The starting materials of Examples 221 and 222 are prepared as follows:

The two diastereomers (3R,4R)-3-{[cyclopropyl-(2-tetrahydro-furan-2(R)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(2-tetrahydro-furan-2(S)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.33 g) on a Chiralpak aD column (20 μM; 5x50 cm) using n-hexane/EtOH/MeOH 80:15:15 as eluent (flow 120 mL/min, UV detection 210 nm).

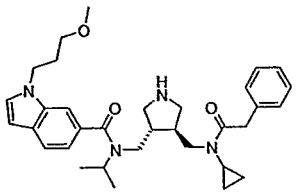
The starting materials of Examples 223 and 224 are prepared as follows:

The two diastereomers (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[cis-(4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[trans-(4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.50 g) on a Chiralpak OD (20 μM; column 5x50 cm) using n-hexane/EtOH/MeOH 97:1.5:1.5 as eluent (flow 120 mL/min, UV detection 210 nm).

The starting materials of Examples 225 and 226 are prepared as follows:

The two diastereomers (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[cis-(4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[trans-(4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.29 mg) on a Chiralpak OD (20 μM; column 5x50 cm) using n-hexane/EtOH/MeOH 97:1.5:1.5 as eluent (flow 120 mL/min, UV detection 210 nm).

Example 227: 1-(3-Methoxy-propyl)-1H-indole-6-carboxylic acid {(3S,4S)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-isopropyl-amide



To a solution of (3R,4R)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.15 g, 0.232 mmol) in dioxane (3 mL), 4N HCl in dioxane (1 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 545.2 $[M+H]^+$; t_R (HPLC, Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min): 2.46 min.

The starting material is prepared in a similar manner as described in Example 149, reaction steps A to E, as follows:

A. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (5 g, 12.9 mmol), 1-(3-methoxy-propyl)-1H-indole-6-carboxylic acid (4.22 g, 18.1 mmol), BOPCl (4.6 g, 18.1 mmol) and triethylamine (7.2 mL, 51.7 mmol). TLC, Rf (AcOEt) = 0.32.

B. (3S,4R)-3-Hydroxymethyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (6.79 g, 11.3 mmol) and TBAF (5.35 g, 17.0 mmol) and purification by flash chromatography on silivca gel (chexane/AcOEt 50:50 to 0:100 to AcOEt/MeOH 90:10). TLC, Rf (AcOEt) = 0.34. MS (LC-MS): 432 $[M+H-tBu]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH3CN/H2O/5 min, 100% CH_3CN/3 min, CH_3CN and H2O containing 0.1% TFA, flow: 1.5 mL/min) : 5.73 min.

C. (3S,4R)-3-Formyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester From (3S,4R)-3-

hydroxymethyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (4.3 g, 8.82 mmol) and Dess Martin Periodinane (4.11 g, 9.70 mmol) to give the title product as a yellow oil which was used in the next step without purification.

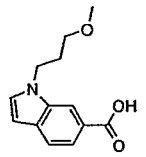
D. (3R,4R)-3-Cyclopropylaminomethyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic

From (3S,4R)-3-formyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (2 g, 4.12 mmol), cyclopropyl amine (0.318 mL, 4.53 mmol) and $NaBHOAc_3$ (1.2 g, 5.77 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5 to CH_2Cl_2/MeOH/NH_4OH 90:10:1). MS (LC-MS): 527.3 $[M+H]^+$; t_R (Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min): 2.45 min.

E. (3R,4R)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4R)-3-cyclopropylaminomethyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic (0.25 g, 0.475 mmol), phenylacethyl chloride (0.069 mL, 0.522 mmol) and triethylamine (0.079 mL, 0.569 mmol) and purification by preparative HPLC (C18-ODB-5 µm, 19x50 mm, eluent: CH_3CN /H_2O + 0.1 % HCOOH). MS (LC-MS): 645.3 $[M+H]^+$; t_R (HPLC, Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min) : 4.11 min.

1-(3-Methoxy-propyl)-1H-indole-6-carboxylic acid



a. 1-(3-Methoxy-propyl)-1H-indole-6-carboxylic acid methyl ester

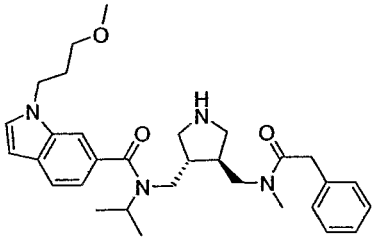
To a solution of methyl indole-6-carboxylate (5.0 g, 28.5 mmol) in DMF (25 mL) is added under nitrogen, NaH-60% dispersion in oil (1.25 g, 31.3 mmol), the mixture is heated at 60°C for 2 h, cooled to RT and 1-bromo-3-methoxypropane (8.7 g, 57.0 mmol) is added. The mixture is further stirred at 60°C overnight. The crude mixture is poured into an aqueous solution of NH_4Cl and diluted with CH_2Cl_2. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are washed with water, dried over Na_2SO_4, filtered and concentrated to give the title product. MS (LC-MS): 248.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.69 min.

b. 1-(3-Methoxy-propyl)-1H-indole-6-carboxylic acid

To a solution of 1-(3-methoxy-propyl)-1H-indole-6-carboxylic acid methyl ester (7 g, 28.5 mmol) in MeOH (50 mL) is added NaOH 2N (28.5 mL), and the mixture is stirred for 3 h. The solvent is concentrated and the remaining aqueous residue is acidified with HCl 1N and extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated to give title product. TLC, R_f (c-hexane/AcOEt 2:1) = 0.25. MS (LC-MS): 232.0 $[M+H]^+$, t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 5.04 min.

The following Example is prepared according to the procedures described above for Example 227:

Table 7

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
228	(3S, 4S)		519.3	2.32

t_R (HPLC, Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min).

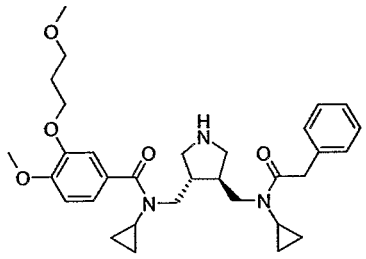
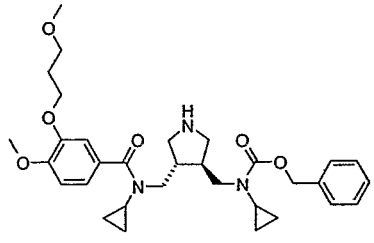
The starting material of the title compound in Table 7 is prepared as follows:

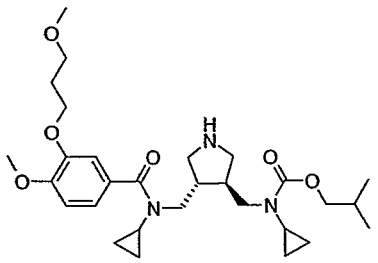
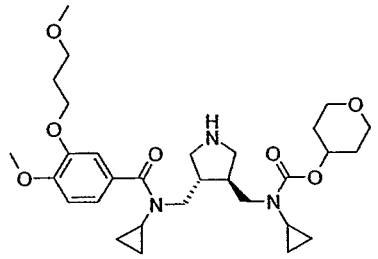
(3R,4R)-3-({Isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

In a similar manner as described in Example 9 for the reaction step J, the following starting material is prepared from (3S,4R)-3-formyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (2 g, 4.12 mmol) (prepared under C in example 229), 2N solution of methylamine in MeOH (10.3 mL, 20.6 mmol) and $NaBH_4$ (0.156 g, 4.12 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5 to CH_2Cl_2/MeOH/NH_4OH 90:10:1). MS (LC-MS): 501.3 $[M+H]^+$; t_R (Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min): 2.40 min.

The following Examples are prepared according to the procedures described above for Examples 227, 233 and 282 using (3R,4R)-3-cyclopropylaminomethyl-4-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

Table 8

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
229	(3S, 4S)		550	3.86
230	(3S, 4S)		565.9	5.16

231	(3S, 4S)		532	5.23
232	(3S, 4S)		560.2	3.33

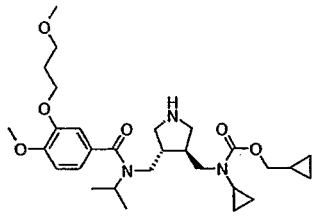
t_R (HPLC, Nucleosil C-18HD, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, flow: 1 ml/min).

The starting material of the title compounds in Table 8 is prepared as follows:

(3R,4R)-3-Cyclopropylaminomethyl-4-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

In a similar manner as described in Example 149 for the reaction step D, the following starting material is prepared from (3R,4S)-3-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (1.79 g, 3.65 mmol) (prepared according to example 9 using cyclopropyl amine instead of isopropyl amine under F), cyclopropyl amine (0.287 mL, 4.01 mmol) and $NaBHOAc_3$ (1.14 g, 5.11 mmol) to give the title compound which is used in the next steps without further purification. TLC, R_f (CH_2Cl_2/AcOEt 9:1) = 0.35. MS (LC-MS): 532.0 $[M+H]^+$.

Example 233 : Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid cyclopropylmethyl ester



To a solution of (3S*,4R*)-3-[(cyclopropyl-cyclopropylmethoxycarbonyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-

carboxylic acid tert-butyl ester (140 mg, 0.222 mmol) in dioxane (4 mL), 4N HCl in dioxane (2 mL) is added and the resulting solution is stirred at RT for 7h. Lyophilization affords the corresponding hydrochloride salt. MS (LC-MS): 532.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.37 min.

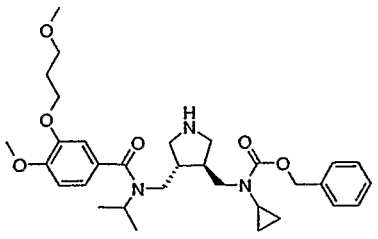
The starting material is prepared as follows:

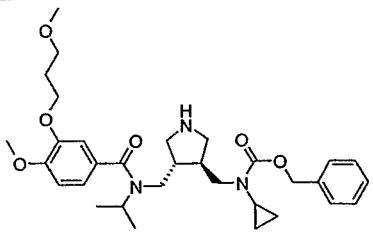
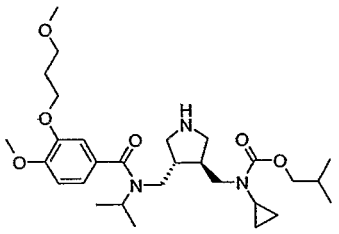
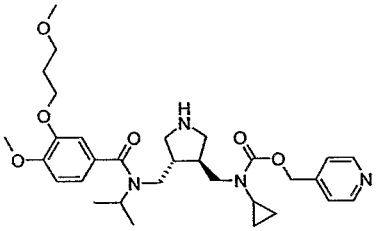
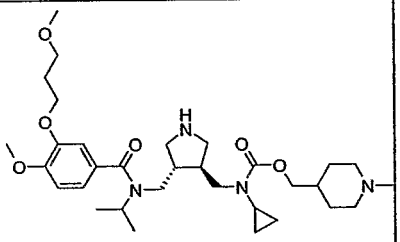
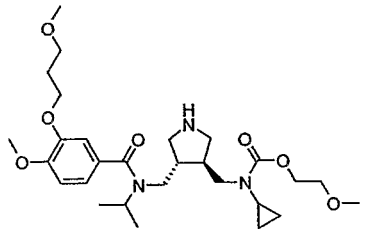
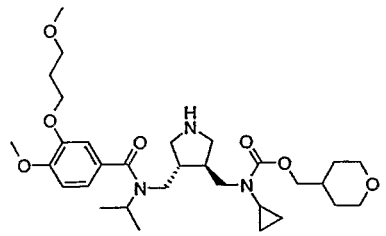
(3S*,4R*)-3-[(Cyclopropyl-cyclopropylmethoxycarbonyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

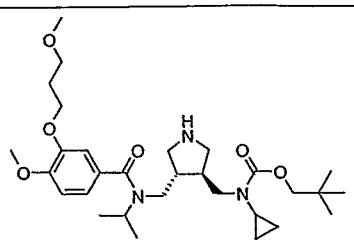
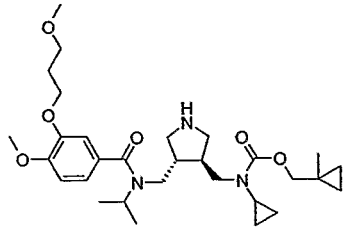
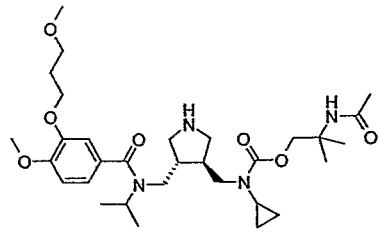
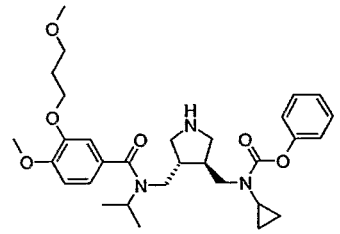
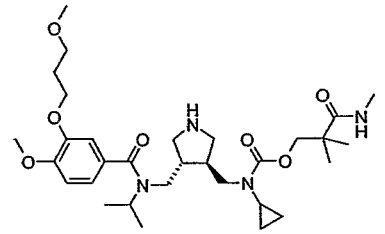
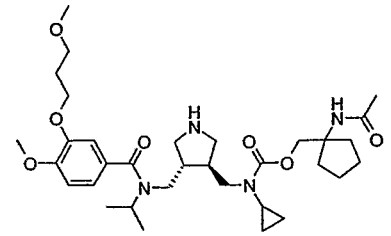
To a solution of cyclopropylmethanol (29µL, 0.366 mmol) in CH_2Cl_2 (5 mL) bis(trichloromethyl) carbonate (40 mg, 0.136 mmol) followed by DMAP (143 mg, 1.170 mmol) are added and the resulting milky suspension is stirred at RT for 15 min. Then a solution of ((3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (215 mg, 0.403 mmol) in CH_2Cl_2 (5 mL) is added and the resulting clear solution is stirred at RT for another 3.5 h. Evaporation of the solvent affords the crude product which is purified by preparative HPLC (Waters C_{18} ODB, eluent: H_2O/CH_3CN 20 to 100%) to give the title compound. MS (LC-MS): 532.0 $[M+H-Boc]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.48 min.

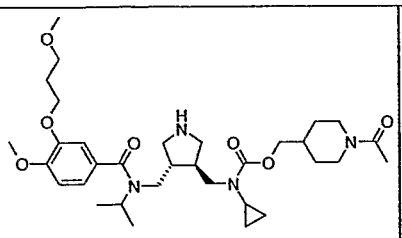
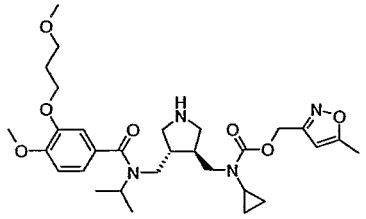
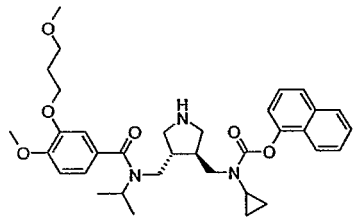
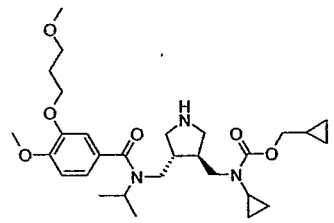
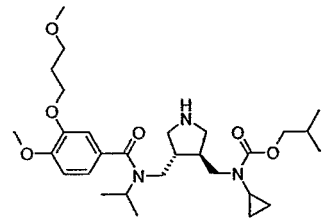
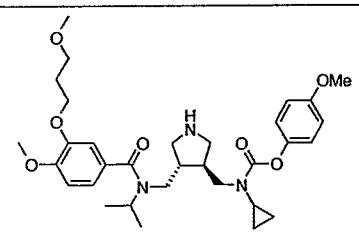
The following Examples are prepared according to the procedures described above for Example 233 or described below for Example 282:

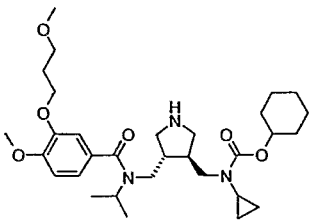
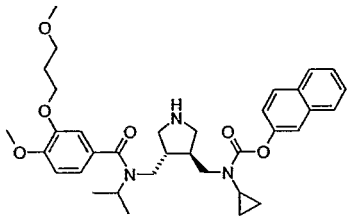
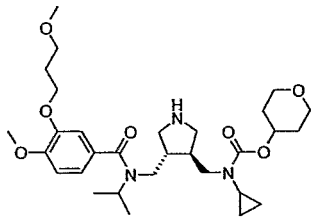
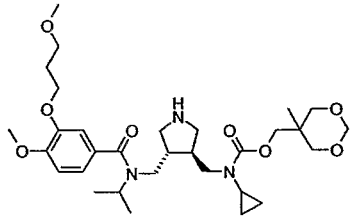
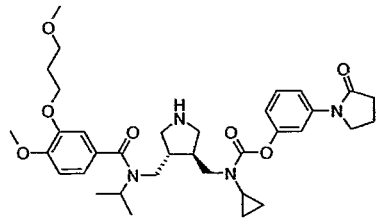
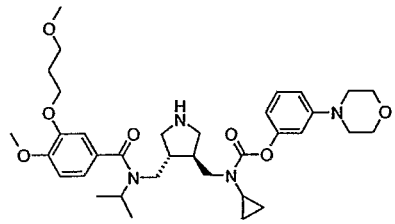
Table 9

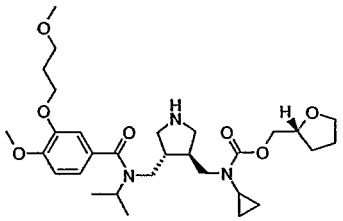
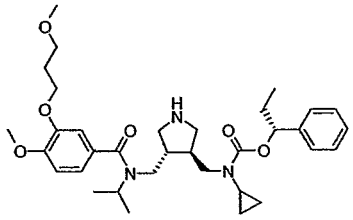
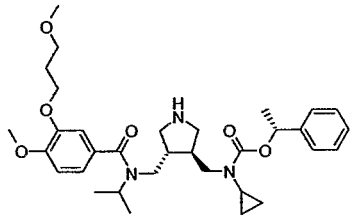
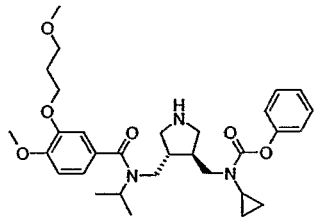
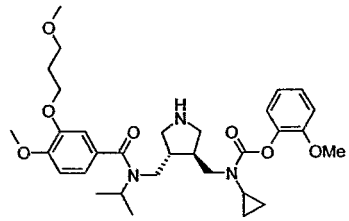
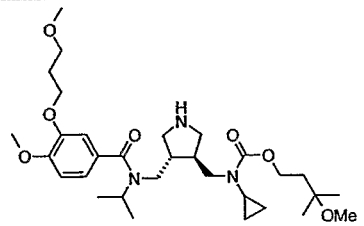
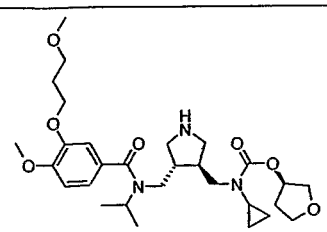
Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
234	(3S*, 4S*)		568.0	5.27[a]

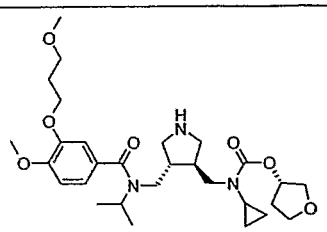
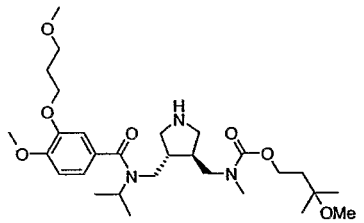
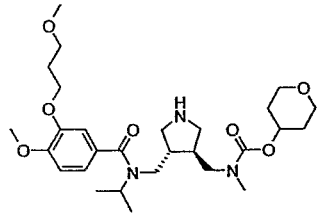
235	(3S, 4S)		568.2	5.17[a]
236	(3S*, 4S*)		534.1	5.35[a]
237	(3S*, 4S*)		285.1 $[M+2H]^{2+}$	4.70[a]
238	(3S*, 4S*)		295.1 $[M+2H]^{2+}$	4.72[a]
239	(3S*, 4S*)		536.0	5.10[a]
240	(3S*, 4S*)		576.1	5.25[a]

241	(3S*, 4S*)		548.1	5.83[a]
242	(3S*, 4S*)		546.1	4.76[a]
243	(3S*, 4S*)		591.4	4.25[a]
244	(3S*, 4S*)		554.3	4.70[a]
245	(3S*, 4S*)		591.4	4.19[a]
246	(3S*, 4S*)		617.4	4.41[a]

247	(3S*, 4S*)		617.5	4.26[a]
248	(3S*, 4S*)		573.4	4.54[a]
249	(3S*, 4S*)		604.2	5.14[a]
250	(3S, 4S)		532.3	4.87[a]
251	(3S, 4S)		534.2	5.11[a]
252	(3S, 4S)		584.2	5.69[a]

253	(3S, 4S)		560.2	5.92[a]
254	(3S, 4S)		604.2	6.01[a]
255	(3S, 4S)		562.3	5.42[a]
256	(3S, 4S)		592.3	5.58[a]
257	(3S, 4S)		637.5	5.88[a]
258	(3S, 4S)		639.2	5.90[a]

259	(3S, 4S)		562.5	5.41[a]
260	(3S, 4S)		596.0	6.35[a]
261	(3S, 4S)		582.0	5.03[a]
262	(3S, 4S)		554.0	4.83[a]
263	(3S, 4S)		584.0	4.85[a]
264	(3S, 4S)		578.5	3.36[b]
265	(3S, 4S)		548.5	3.08[b]

266	(3S, 4S)		548.4	0.38[b]
267	(3S, 4S)		552.2	4.44[a]
268	(3S, 4S)		536.2	2.58[c]

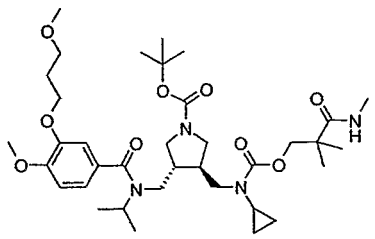
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 10-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[c] t_R (Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

The starting material of Example 245 is prepared as follows:

(3S*,4R*)-3-{[Cyclopropyl-(2-methyl-2-methylcarbamoyl-propoxycarbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester



HBTU (161 mg, 0.43 mmol) is added to a solution of (3S*,4R*)-3-{[(2-carboxy-2-methyl-propoxycarbonyl)-cyclopropyl-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (240 mg, 0.35

mmol) in CH_3CN (10 mL) at 0°C. After 5 min a solution of methylamine (44 µL, 0.35 mmol, 8M in EtOH) and triethylamine (493 µL, 3.54 mmol) in CH_3CN (10 mL) is added at 0°C and the reaction solution is stirred at RT for 5 h. Another portion of methylamine (0.22 mL, 1.75 mmol) is added and stirring is continued for another 16 h. Then, triethylamine (247 µL, 1.77 mmol) and HBTU (268 mg, 1.02 mmol) are added and the reaction mixture is stirred at 50°C for another 16 h. The solvent is evaporated and the crude product purified by HPLC (Interchrom C_{18} ODB 10 µm, 28x250 mm, eluent: CH_3CN/H_2O 5%/2.5 min, CH_3CN/H_2O 5-100%/23 min, 100% CH_3CN/4.5 min, flow 40 mL/min) to give the title compound. MS (LC-MS): 691.4 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.38 min.

The starting material is prepared as follows:

A. (3S*,4R*)-3-{[Cyclopropyl-(2-methoxycarbonyl-2-methyl-propoxycarbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described above for NVP-BGW706 from ((3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and methyl 2,2-dimethyl-3-hydroxypropionate using bis(trichloromethyl) carbonate. MS (LC-MS): 592.1 $[M+H-Boc]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.92 min.

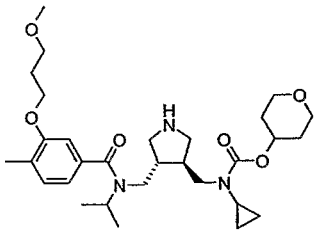
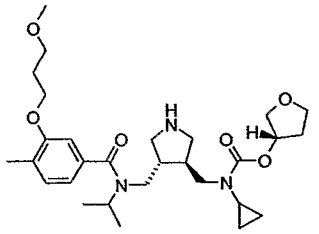
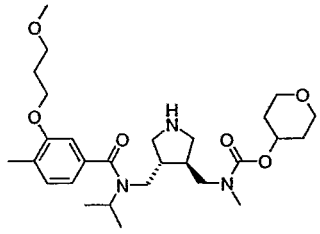
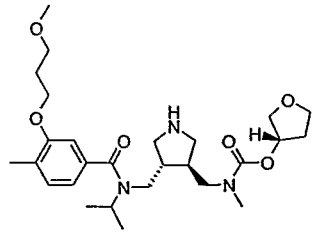
B. (3S*,4R*)-3-{[(2-Carboxy-2-methyl-propoxycarbonyl)-cyclopropyl-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

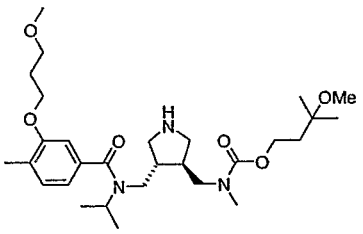
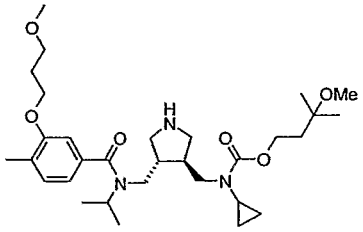
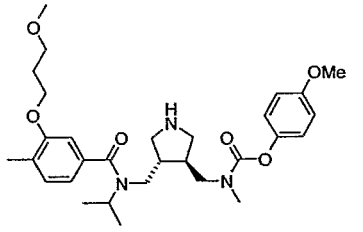
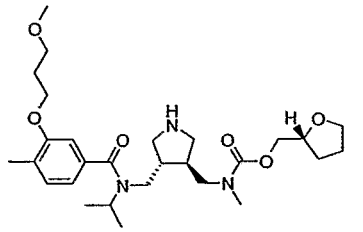
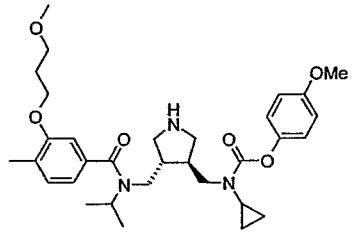
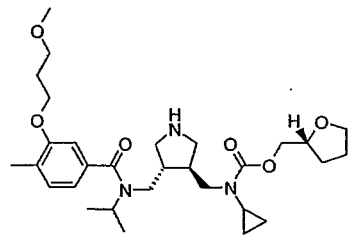
A mixture of (3S*,4R*)-3-{[cyclopropyl-(2-methoxycarbonyl-2-methyl-propoxycarbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (290 mg, 0.42 mmol) and $LiOH \bullet .H_2O$ (44 mg, 1.05 mmol) in H_2O (2 mL) and THF (6 mL) is stirred at RT for 3 d. After evaporation of the solvent 1N HCl is added and the mixture is extracted with ethyl acetate. Drying (Na_2SO_4) of the combined extracts, filtration and evaporation of the solvent affords the title compound which is used without further purification. MS (LC-MS): 578.0 $[M+H-Boc]^+$; t_R (HPLC,

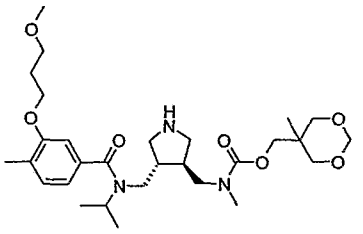
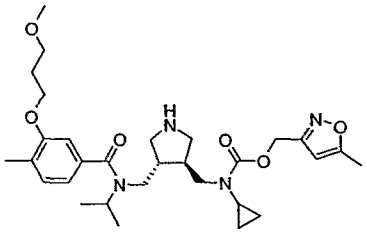
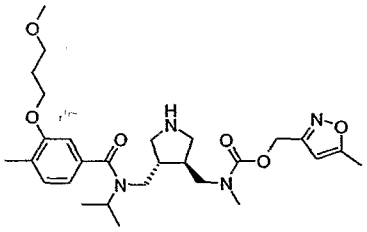
Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.44 min.

The following Examples are prepared according to the procedures described above for Example 233 or below for Example 282 using (3R,4R)-3-cyclopropylaminomethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester or (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester:

Table 10

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
269	(3S, 4S)		546.3	5.76[a]
270	(3S, 4S)		532.3	4.71[a]
271	(3S, 4S)		520.3	4.57[a]
272	(3S, 4S)		506.2	4.52[a]

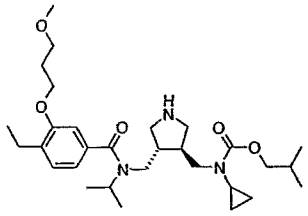
273	(3S, 4S)		536.3	2.64[b]
274	(3S, 4S)		562.3	5.03[a]
275	(3S, 4S)		542.2	5.00[a]
276	(3S, 4S)		520.3	4.67[a]
277	(3S, 4S)		568.3	5.18[a]
278	(3S, 4S)		546.3	4.85[a]

279	(3S, 4S)		550.3	4.74[a]
280	(3S, 4S)		557.2	2.68[b]
281	(3S, 4S)		531.1	2.51[b]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

Example 282 : Cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid isobutyl ester



To a solution of (3S,4R)-3-[(cyclopropyl-isobutoxycarbonyl-amino)-methyl]-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.280 g, 0.443 mmol) in dioxane (2 mL), 4N HCl in dioxane (2 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 532 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.52 min.

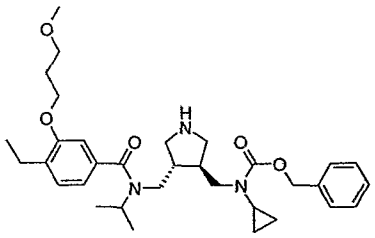
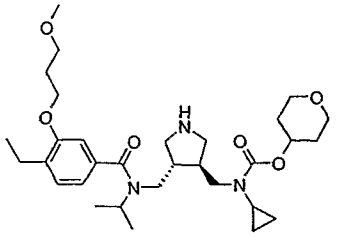
The starting material is prepared as follows:

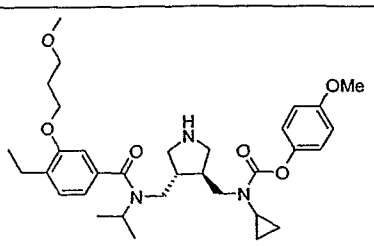
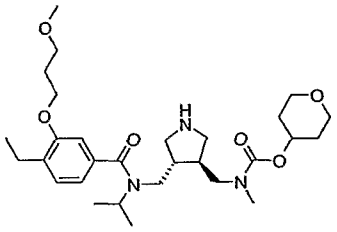
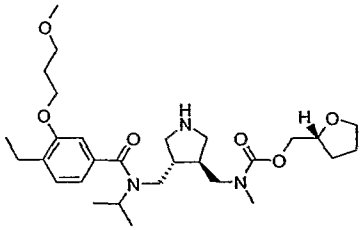
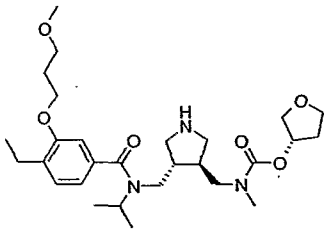
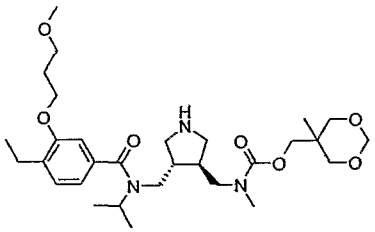
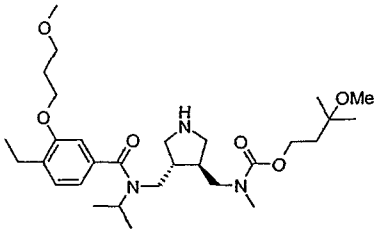
(3S,4R)-3-[(Cyclopropyl-isobutoxycarbonyl-amino)-methyl]-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R,4R)-3-cyclopropylaminomethyl-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (250 mg, 0.470 mmol) in CH_2Cl_2 (3 mL) are added isobutylchloroformate (84 mg, 0.611 mmol) and triethylamine (85 µL, 0.611 mmol) under a N_2 atmosphere. The mixture is stirred overnight at RT, diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude residue is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 90:10) to give the title compound. MS (LC-MS): 532 $[M+H\text{-}Boc]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 8.22 min.

The following Examples are prepared according to the procedures described above for Example 233 or Example 282:

Table 11

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
283	(3S, 4S)		556	5.53[a]
284	(3S, 4S)		560.3	2.68[b]

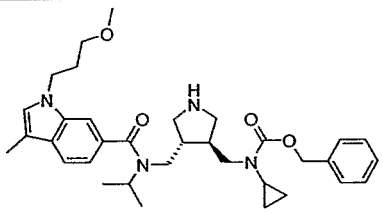
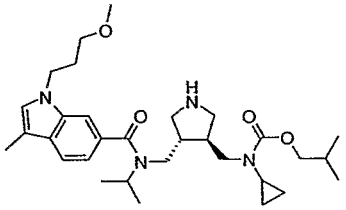
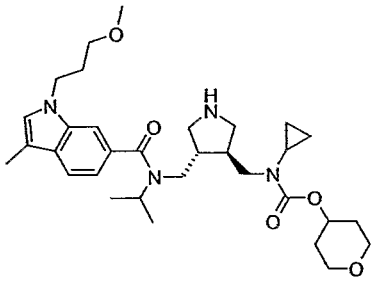
285	(3S, 4S)		582.2	2.95[b]
286	(3S, 4S)		534.2	4.80[a]
287	(3S, 4S)		534.2	4.87[a]
288	(3S, 4S)		520.3	4.73[a]
289	(3S, 4S)		564.3	4.91[a]
290	(3S, 4S)		550.2	2.80[b]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

The following Examples are prepared according to the procedures described above for Example 233 or Example 282 using (3R,4R)-3-cyclopropylaminomethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

Table 12

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
291	(3S, 4S)		575	5.67[a]
292	(3S, 4S)		541	5.66[a]
293	(3S, 4S)		569.3	4.22[b]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (HPLC, Nucleosil C-18HD (4x70mm, 3µm), 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/ 1.5 min; flow: 1 mL/min).

N-(2-Hydroxy-1,1-dimethyl-ethyl)-acetamide

A mixture of 2-amino-2-methyl-propan-1-ol (2.0 mL, 20.4 mmol), acetanhydride (1.9 mL, 20.4 mmol) and $NaHCO_3$ (2.6 g, 30.6 mmol) in H_2O (20 mL) is stirred at RT for 16 h. For

workup 1N HCl is added and the mixture is extracted with ethyl acetate. Drying (Na_2SO_4) of the combined extracts, filtration and evaporation of the solvent yields the title compound as a colorless solid. MS (LC-MS): $[M+H]^+$= 132.2. t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.38 min.

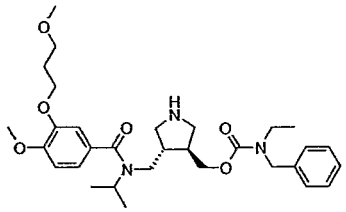
N-(1-Hydroxymethyl-cyclopentyl)-acetamide

The title compound is prepared analogously as described for N-(2-hydroxy-1,1-dimethyl-ethyl)-acetamide from (1-amino-cyclopentyl)-methanol. MS (LC-MS): $[M+H]^+$= 158.2. t_R (HPLC, Waters sun fire C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.8 mL/min): 1.76 min.

1-(4-Hydroxymethyl-piperidin-1-yl)-ethanone

The title compound is prepared analogously as described for N-(2-hydroxy-1,1-dimethyl-ethyl)-acetamide from piperidin-4-yl-methanol. MS (LC-MS): $[M+H]^+$= 158.3. t_R (HPLC, Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.39 min.

Example 294 : Benzyl-ethyl-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester



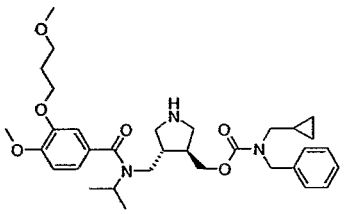
To a solution of (3S,4R)-3-[(benzyl-ethyl-carbamoyloxy)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (83 mg, 0.127 mmol) in 2 mL dioxane, 4 N HCl in dioxane (1 mL, 4 mmol) is added. The mixture is stirred at RT for 2 h, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 556.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.89 min.

The starting material is prepared as follows:

(3S,4R)-3-[(Benzyl-ethyl-carbamoyloxy)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a stirred solution of (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (250 mg, 0.505 mmol) in CH_2Cl_2 (10 mL) is added triphosgen (56 mg, 0.187 mmol) and DMAP (197 mg, 1.62 mmol). The resulting solution is stirred 30 min before the addition of commercially available N-ethylbenzylamine (113 µL, 0.758 mmol). The mixture is further stirred overnight, then diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 98:2). TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.2. MS (LC-MS): 655.9 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.36 min.

Example 295 : Benzyl-cyclopropylmethyl-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester



The title compound is prepared analogously as described in Example 294 from (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and benzyl-cyclopropylmethyl-amine. MS (LC-MS): 582.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.15 min.

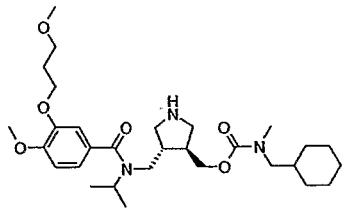
The starting material is prepared as follows:

Benzyl-cyclopropylmethyl-amine

A mixture of benzaldehyde (3 mL, 29.55 mmol), cyclopropanemethylamine (2.53 mL, 29.55 mmol), AcOH (1.7 mL, 29.55 mmol) in 1,2-dichloroethane (150 mL) is stirred at RT for 25 minutes. Sodium triacetoxyborohydride (8.8 g, 41.37 mmol) is added and the mixture further

stirred overnight at RT. Sodium triacetoxyborohydride (3.13 g, 15 mmol) is again added to complete the reaction. The mixture is quenched by the addition of NaOH 1N (50 mL), the layers are separated and the aqueous phase is extracted twice with ether. The combined organic extracts are dried (Na_2SO_4), filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 95:5 to 80:20+ 5% NH_3) to give the title product. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.91 min.

Example 296: Cyclohexylmethyl-methylcarbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxypropoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-yl-methyl ester



To a solution of (3S,4R)-3-[(cyclohexylmethyl-methyl-carbamoyloxy)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (182 mg, 0.281 mmol) in 1 mL dioxane, 4 N HCl in dioxane (2 mL, 8 mmol) is added. The mixture is stirred at RT for 2 h, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 548 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.14 min.

The starting material is prepared as follows:

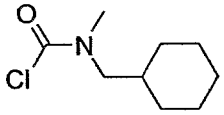
(3S,4R)-3-[(cyclohexylmethyl-methyl-carbamoyloxy)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a stirred suspension of NaH (60% oily dispersion, 17 mg, 0.42 mmol) in THF (2 mL) is added at 0°C (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (160 mg, 0.303 mmol) in THF (3 mL). The resulting solution is stirred 30 min before the addition of a solution of cyclohexylmethyl-methyl-carbamoyl chloride (80 mg, 0.421 mmol) in THF (3 mL). The mixture is further stirred overnight at RT and poured into an aqueous solution of NH_4Cl.

AcOEt is added, the layers are separated and the aqueous one extracted twice with AcOEt. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 95:5). TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.25. MS (LC-MS): 648 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.83 min.

Intermediates are prepared as described by the following methods:

Cyclohexylmethyl-methyl-carbamoyl chloride



a. Cyclohexylmethyl-methyl-amine

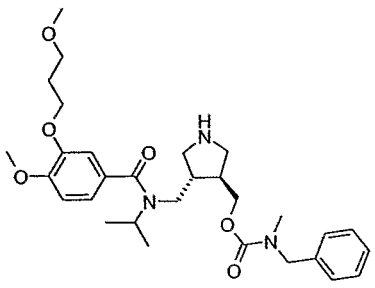
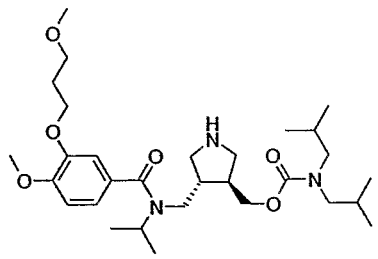
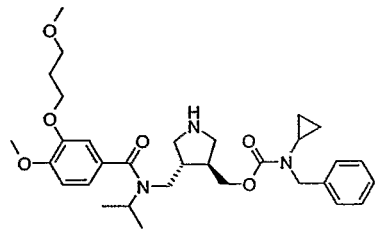
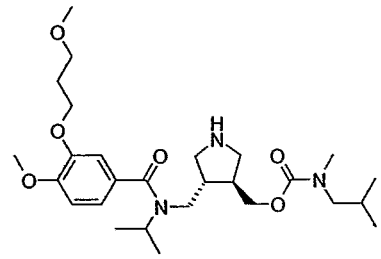
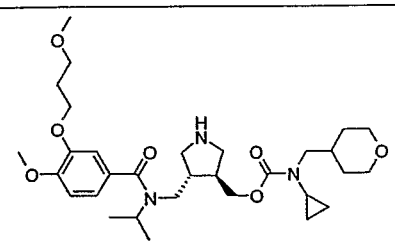
A solution of cyclohexancarbaldehyde (4 mL, 33.24 mmol) and methylamine (50.0 mL, 99.8 mmol) in MeOH (160 mL containing 2% AcOH) is stirred at RT for 1 h. Sodium borohydride (2.515 g, 66.48 mmol) is added portionwise at 0°C and stirring is continued, at RT for 1 h. A solution of NaOH 1N is added and the methanol is concentrated. CH_2Cl_2 is added, the layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography (eluent: CH_2Cl_2/MeOH 95:5 to 80:20+ 5% NH_3) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 7.09 min.

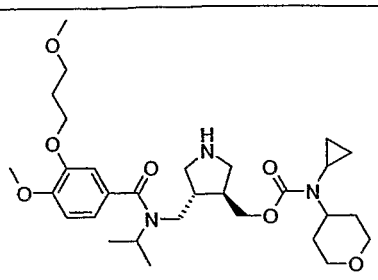
b. Cyclohexylmethyl-methyl-carbamoyl chloride

To a solution of triphosgene (77 mg, 0.259 mmol) in CH_2Cl_2 (1 mL) at - 78°C is added dropwise pyridine (63 µl, 0.786 mmol) followed by a solution of cyclohexylmethyl-methyl-amine (100 mg, 0.786 mmol) in CH_2Cl_2 (1 mL). The yellow mixture is allowed to reach RT and stirred overnight. The solvent is concentrated, and the residue taken up in AcOEt. An aqueous saturated solution of $NaHCO_3$ is added, the layers are separated and the aqueous one is extracted twice with AcOEt. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated to afford the title compound as a yellow oil. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.95. MS (LC-MS): 189.1 $[M+H]^+$.

The following Examples are prepared according to the procedures described above for Example 296 :

Table 13

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
297	(3S*, 4S*)		542.5	4.70[a]
298	(3S, 4S)		550	5.33[a]
299	(3S, 4S)		568	4.15[a]
300	(3S, 4S)		508	5.13[a]
301	(3S, 4S)		576.3	4.44[a]

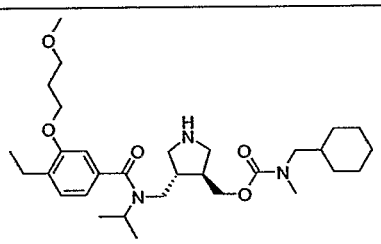
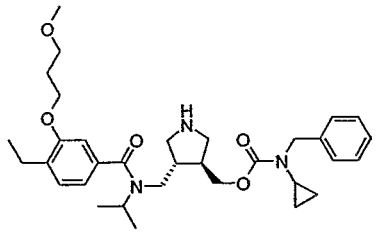
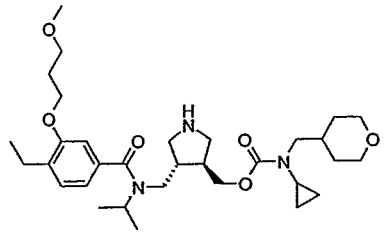
302	(3S, 4S)		562.3	1.07[b]

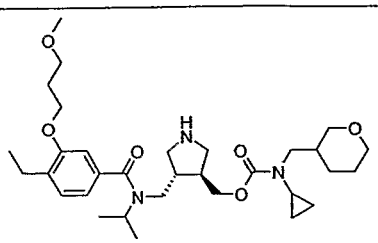
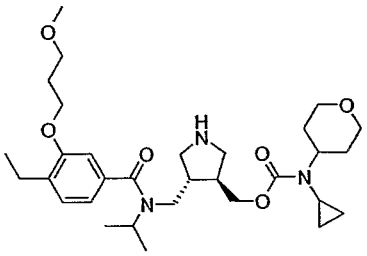
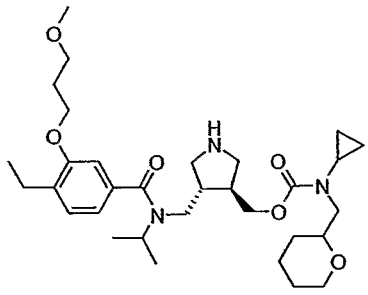
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (HPLC Zorbax SB C18, 10-95% CH_3CN/H_2O/0.8 min, 95% CH_3CN/0.7 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 1.5 ml/min).

The following Examples are prepared according to the procedures described above for Example 296 using (3R,4S)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester:

Table 14

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
303	(3S, 4S)		546.6	5.41[b]
304	(3S, 4S)		566.6	5.10[b]
305	(3S, 4S)		574.4	5.02[a]

306	(3S, 4S)		574.2	5.04 [b] 5.13 [b]
307	(3S, 4S)		560.3	4.94[a]
308	(3S, 4S)		574.2	4.87[b]

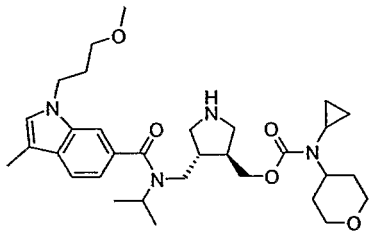
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min). ou 1.5 de flux attendre reponse anne

[b] t_R (HPLC, Nucleosil C18-HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, flow: 1 ml/min).

The following Examples are prepared according to the procedures described above for Example 296 starting from (3S,4R)-3-hydroxymethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

Table 15

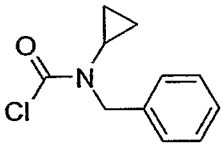
Example	configuration	structure	$[M+H]^+$	t_R (HPLC)

309	(3S, 4S)		569.3	2.39

t_R (HPLC, Waters Symmetry C18 column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min).

Intermediates are prepared as described by the following methods:

Benzyl-cyclopropyl-carbamoyl chloride



a. Benzyl-cyclopropyl-amine

The title compound is prepared analogously as described for benzyl-cyclopropylmethyl-amine. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1, MS (LC-MS): 148.2 $[M+H]^+$.

b. Benzyl-cyclopropyl-carbamoyl chloride

The title compound is prepared analogously as described for cyclohexylmethyl-methyl-carbamoyl chloride. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9. MS (LC-MS): $[M+H]^+$= 210.2. t_R (HPLC, Waters Symmetry C18 column, 20-100% CH_3CN/H_2O/5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.67 min.

Cyclopropyl-(tetrahydro-pyran-4-ylmethyl)-carbamoyl chloride

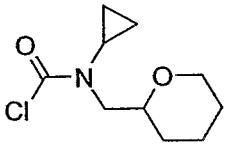
The title compound is prepared analogously as described for benzyl-cyclopropyl-carbamoyl chloride starting from cyclopropyl-(tetrahydro-pyran-4-ylmethyl)-amine (prepared analogously as described for benzyl-cyclopropylmethyl-amine). TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9.

Cyclopropyl-(tetrahydro-pyran-3-ylmethyl)-carbamoyl chloride

The title compound is prepared analogously as described for benzyl-cyclopropyl-carbamoyl chloride starting from cyclopropyl-(tetrahydro-pyran-3-ylmethyl)-amine (prepared

analogously as described for benzyl-cyclopropylmethyl-amine). TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9.

Cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-carbamoyl chloride



a. Toluene-4-sulfonic acid tetrahydro-pyran-2-ylmethyl ester

To a suspension of tetrahydropyran-2-methanol (2 g, 17.2 mmol) cooled at 0°C is added toluene-4-sulfonyl chloride (3.6 g, 18.92 mmol), followed by (2.63 mL , 18.92 mmol) of triethylamine. The mixture is allowed to reach RT and stirred overnight. Then poured into an aqueous saturated solution of $NaHCO_3$. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 80:20) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9. MS (LC-MS): 271.1 $[M+H]^+$, t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 5.32 min.

b. Cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-amine

A mixture of toluene-4-sulfonic acid tetrahydro-pyran-2-ylmethyl ester (500 mg, 1.85 mmol) and cyclopropylamine (2 mL, 15 mmol) is heated overnight at 110 °C in a sealed tube. The crude mixture is concentrated and taken up in CH_2Cl_2. Water is added, the layers are separated and the aqueous one back extracted twice with CH_2Cl_2. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3, MS (LC-MS): 156.2 $[M+H]^+$.

c. Cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-carbamoyl chloride

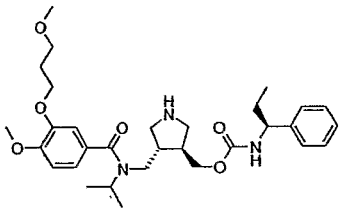
To a stirred solution of cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-amine (200 mg, 0.74 mmol) in THF (4 mL) is added triethylamine (144 µL, 1.036 mmol) and 4-dimethylaminopyridine (1.81 mg, 0.015 mmol). The mixture is cooled to 0°C, and triphosgene (88 mg, 0.296 mmol) is added in one portion. After stirring for 30 min at 0°C and overnight at RT, water is cautiously added and the solution is extracted with AcOEt. The combined organic extracts

are washed with brine, dried over Na_2SO_4, filtered and concentrated. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9.

Cyclopropyl-(tetrahydro-pyran-4-yl)-carbamoyl chloride

The title compound is prepared analogously as described for cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-carbamoyl chloride starting from commercially available cyclopropyl-(tetrahydro-pyran-4-yl)-amine. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9.

Example 310 : ((S)-1-Phenyl-propyl)-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester



To a solution of (3R,4S)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-((S)-1-phenyl-propylcarbamoyloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (49 mg, 0.075 mmol) in 1 mL dioxane, 4 N HCl in dioxane (0.5 mL, 2 mmol) is added. The mixture is stirred at RT for 2 h, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 556.3 $[M+H]^+$; t_R (HPLC, Nucleosil C18-HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, flow: 1 ml/min): 4.11 min.

The starting material is prepared as follows:

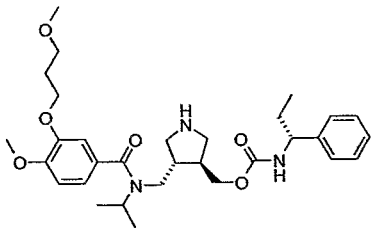
(3R,4S)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-((S)-1-phenyl-propylcarbamoyloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (200 mg, 0.404 mmol) in ether (12 mL) are successively added (S)-1-phenylpropyl isocyanate (130.4 mg, 0.809 mmol) and $AlCl_3$ (54 mg, 0.404 mmol). The mixture is stirred at RT under nitrogen overnight. (S)-1-phenylpropyl isocyanate (150 µL) and $AlCl_3$ (54 mg, 0.404 mmol) are again added and the mixture further stirred for 5 h. AcOEt is added and the reaction mixture quenched by the addition of an aqueous saturated solution of $NaHCO_3$. The layers are separated and the aqueous one back extracted twice with AcOEt. The combined organic extracts are dried over

Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 95:5) to give the title product TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.35. MS (LC-MS): 656.2 $[M+H]^+$; t_R (HPLC, Nucleosil C18-HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, flow: 1 ml/min): 3.94 min.

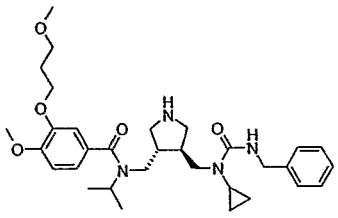
The following Examples are prepared according to the procedures described above for Example 310 :

Table 16

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
311	(3S, 4S)		556.3	4.13

t_R (HPLC, Nucleosil C18-HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, flow: 1 ml/min).

Example 312: N-[(3S*,4S*)-4-(3-Benzyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

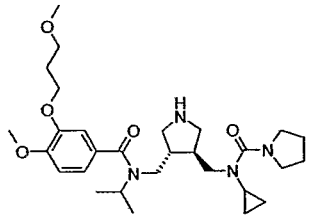


To a solution of (3R*,4R*)-3-(3-benzyl-1-cyclopropyl-ureidomethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (270 mg, 0.405 mmol) in dioxane (5 mL), 4N HCl in dioxane (3 mL) is added and the resulting solution is stirred at RT for 5 h. Lyophilization affords the corresponding hydrochloride salt as a colorless powder. MS (LC-MS): 567.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.18 min.

The starting material is prepared as follows:

(3R*,4R*)-3-(3-Benzyl-1-cyclopropyl-ureidomethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester To a solution of ((3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (235 mg, 0.440 mmol) in THF (6 mL) is added triethylamine (123 µL, 0.880 mmol) followed by benzylisocyanate (54 µL, 0.440 mmol). The mixture is stirred at RT for 2 h before water is added. Extraction with ethyl acetate, drying of the combined extracts (Na_2SO_4), filtration and evaporation of the solvent affords the crude product which is purified by flash chromatography on silica gel (eluent gradient: CH_2Cl_2 100% to CH_2Cl_2/MeOH 9:1) to give the title compound. MS (LC-MS): 667.1M+H]$^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.26 min.

Example 313: Pyrrolidine-1-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide



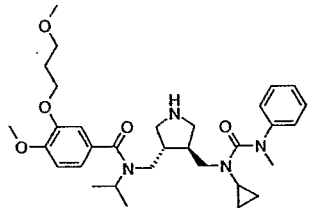
To a solution of (3R*,4R*)-3-{[cyclopropyl-(pyrrolidine-1-carbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (165 mg, 0.262 mmol) in dioxane (5 mL), 4N HCl in dioxane (3 mL) is added and the resulting solution is stirred at RT for 4.5 h. Lyophilization affords the corresponding hydrochloride salt as a colorless solid. MS (LC-MS): 531.1 [M+H]$^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.11 min.

The starting material is prepared as follows:

(3R*,4R*)-3-{[Cyclopropyl-(pyrrolidine-1-carbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Triethylamine (99 µL, 0.714 mmol) followed by 1-pyrrolidinecarbonyl chloride is added to a solution of ((3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (254 mg, 0.476 mmol) in CH_2Cl_2 (20 mL). The resulting solution is stirred at RT for 2 h and at 60°C for another 24 h. Evaporation of the solvent affords the crude product which is purified by preparative HPLC (Waters C_{18} ODB, eluent: H_2O/CH_3CN 20 to 100%) to give the title compound. MS (LC-MS): 631.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.31 min.

Example 314: N-[(3S*,4S*)-4-(1-Cyclopropyl-3-methyl-3-phenyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide



A solution of (3R*,4R*)-3-(1-cyclopropyl-3-methyl-3-phenyl-ureidomethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (195 mg, 0.29 mmol) in 4N HCl/dioxane (8 mL) is stirred at RT until the reaction is complete. Lyophilization affords the title compound as a colorless foam. MS (LC-MS): 567.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 4.57 min.

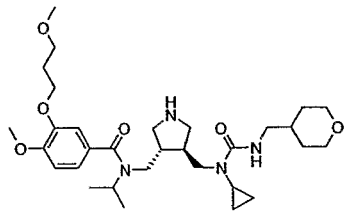
The starting material is prepared as follows:

(3R*,4R*)-3-(1-Cyclopropyl-3-methyl-3-phenyl-ureidomethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (216 mg, 0.41 mmol), N-methyl-N-phenyl carbamoylchloride (274 mg, 1.62 mmol), triethylamine (0.45 mL,

3.24 mmol) and DMAP (1 mg, 0.008 mmol) in THF (15 mL) is heated at 60°C for 4 h. After cooling to RT 1N HCl is added and the mixture is extracted with ethyl acetate, the combined organic extracts are dried (Na_2SO_4), filtered and the solvent is evaporated. Purification by flash chromatography on silica gel (eluent gradient: CH_2Cl_2 100% CH_2Cl_2/MeOH 9:1) affords the title compound. MS (LC-MS): 667.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.02 min.

Example 315 N-{(3S,4S)-4-[1-Cyclopropyl-3-(tetrahydro-pyran-4-ylmethyl)-ureido-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy) -benzamide



To a solution of (3R*,4R*)-3-[1-cyclopropyl-3-(tetrahydro-pyran-4-ylmethyl)-ureidomethyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (50 mg, 0.074 mmol) in dioxane (3 mL), 4N HCl in dioxane (1 mL) is added and the resulting solution is stirred at RT for 5 h. Lyophilization affords the corresponding hydrochloride salt as a colorless solid. MS (LC-MS): 575.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.29 min.

The starting material is prepared as follows:

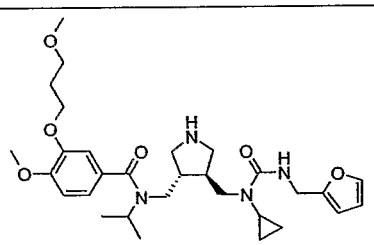
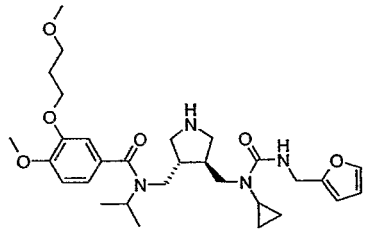
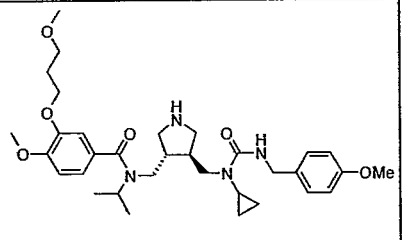
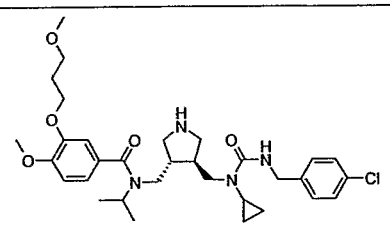
(3R*,4R*)-3-[1-Cyclopropyl-3-(tetrahydro-pyran-4-ylmethyl)-ureidomethyl]-4-({iso-propyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

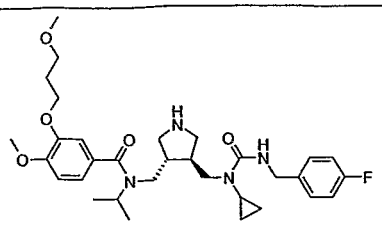
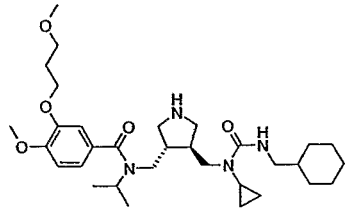
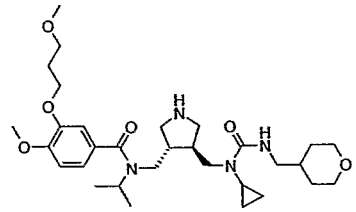
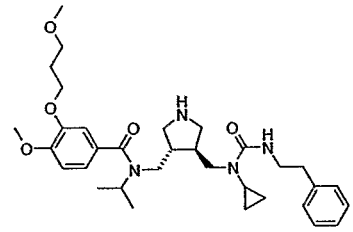
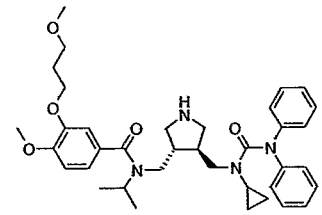
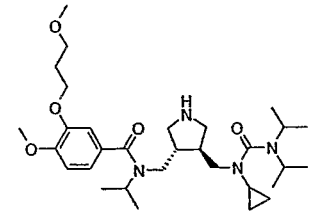
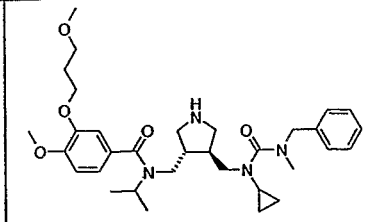
4-Aminomethyl tetrahydropyrane (50 mg, 0.435 mmol) is added to a suspension of bis(trichloromethyl) carbonate (155 mg, 0.522 mmol) and charcoal (10 mg) in AcOEt(8 mL) at RT. The mixture is stirred at RT for 5 min and heated under reflux for another 10 min before it is allowed to cool to RT. Filtration and evaporation of the solvent affords the corresponding isocyanate which is used without further purification and dissolved in CH_3CN (10 mL). ((3R*,4R*)-3-Cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-

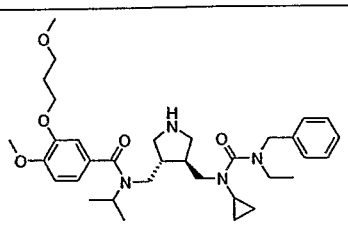
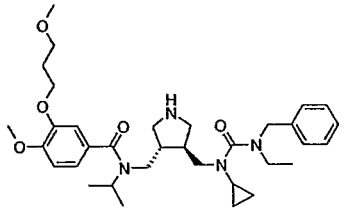
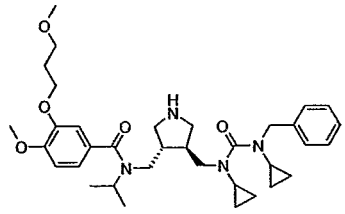
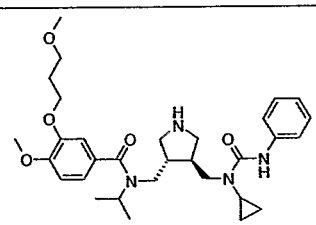
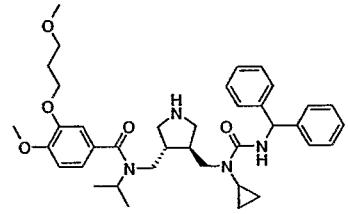
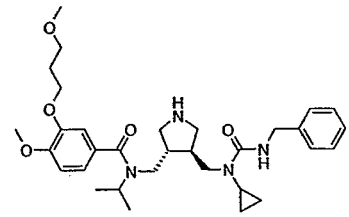
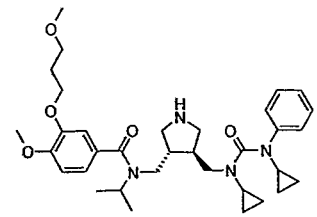
propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (232 mg, 0.435 mmol) is added and the mixture is heated under reflux for 16 h. For workup the solvent is evaporated and purified by preparative HPLC (Interchrom C_{18} ODB, eluent: CH_3CN/H_2O 5%/2.5 min, CH_3CN/H_2O 5-100%/22.5 min, 100% CH_3CN/4.5 min, flow 40 mL/min) to give the title compound. MS (LC-MS): 675.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.19 min.

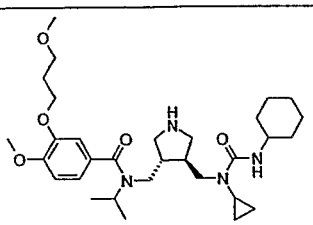
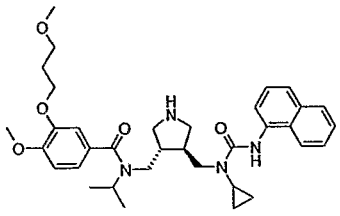
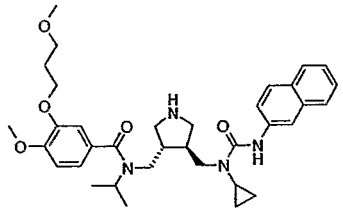
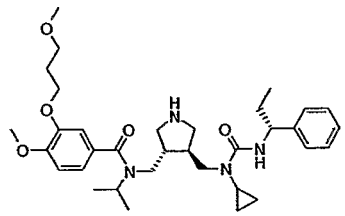
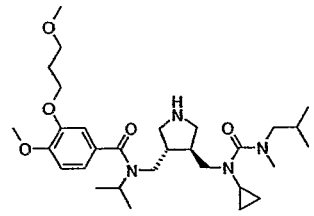
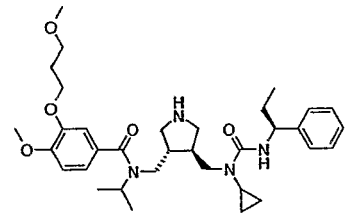
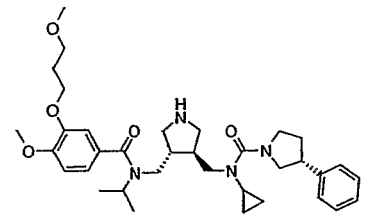
The following Examples are prepared according to the procedures described above for Example 312 or Example 314:

Table 17

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
316	(3S*, 4S*)		557.0	5.17[a]
317	(3S, 4S)		557.5	4.77[a]
318	(3S*, 4S*)		597.1	5.35[a]
319	(3S*, 4S*)		601.0	5.58[a]

320	(3S*, 4S*)		585.0	5.42[a]
321	(3S*, 4S*)		573.1	5.73[a]
322	(3S*, 4S*)		575.1	5.29[a]
323	(3S*, 4S*)		581.1	5.67[a]
324	(3S*, 4S*)		629.1	5.85[a]
325	(3S*, 4S*)		561.1	5.70[a]
326	(3S*, 4S*)		581.1	4.66[a]

327	(3S*, 4S*)		595.1	4.78[a]
328	(3S, 4S)		595.0	5.04[a]
329	(3S*, 4S*)		607.5	4.96[a]
330	(3S*, 4S*)		553.3	4.74[a]
331	(3S*, 4S*)		643.2	5.17[a]
332	(3S, 4S)		567.3	4.82[a]
333	(3S*, 4S*)		593.3	4.94[a]

334	(3S*, 4S*)		559.5	5.05[a]
335	(3S*, 4S*)		603.3	5.52[a]
336	(3S, 4S)		603.3	5.95[a]
337	(3S, 4S)		595.2	5.85[a]
338	(3S, 4S)		547.2	5.91[a]
339	(3S, 4S)		595.2	5.13[a]
340	(3S, 4S)		607.5	3.47[b]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (HPLC, Waters Symmetry C18 column, 10-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

Benzyl-methyl-carbamoyl chloride

At -78°C pyridine (1.25 mL, 15.5 mmol) followed by methyl benzylamine (2.0 mL, 15.5. mmol) are added to a solution of bis(trichloromethyl) carbonate (1.55 g, 5.2 mmol) in CH_2Cl_2 (20 mL). The reaction mixture is allowed to warm to RT and stirred for another 1.5 h. For workup 1N HCl is added to the yellow suspension and the mixture is extracted with ethyl acetate. Drying (Na_2SO_4) of the combined organic exctracts, filtration and evaporation of the solvent affords the title compound. MS (LC-MS): $[M+H]^+$= 184.1. t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 3.84 min.

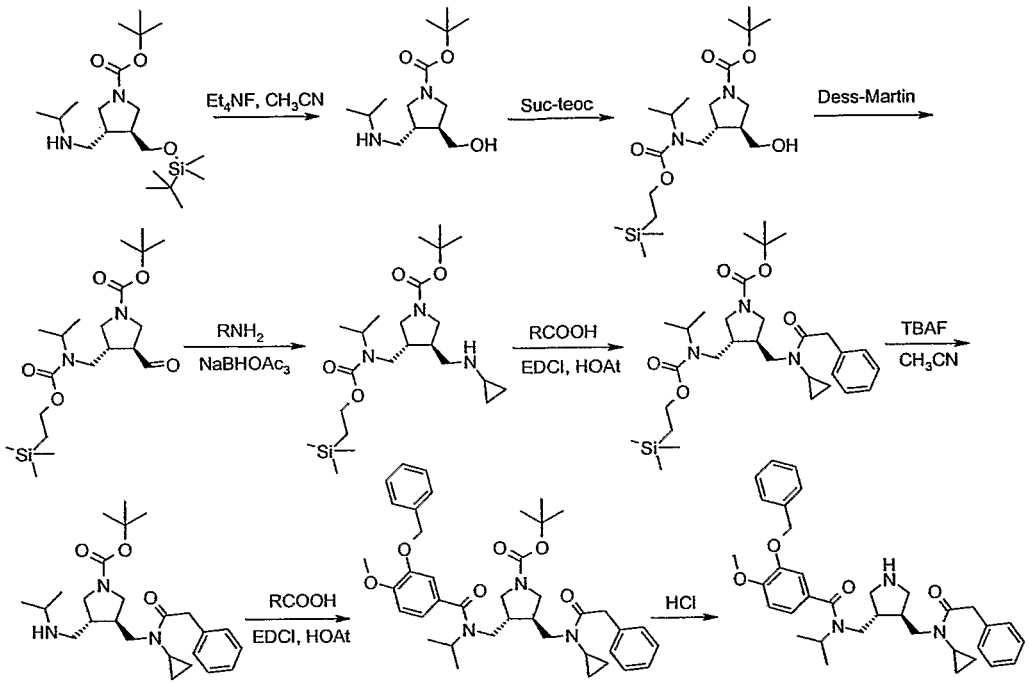
Benzyl-ethyl-carbamoyl chloride

The title compound is prepared analogously as described for benzyl-methyl-carbamoyl chloride from benzyl ethylamine. MS (LC-MS): $[M+H]^+$= 198.1. t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.12 min.

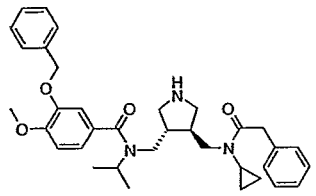
Phenyl-cyclopropyl-carbamoyl chloride

The title compound is prepared analogously as described for benzyl-methyl-carbamoyl chloride from cyclopropyl-phenyl-amine prepared according to Synlett **2003**, *14*, 2139. MS (LC-MS): $[M+H]^+$= 196.2. t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.44 min.

Scheme 6



Example 341: 3-Benzyloxy-N-{(3S,4S)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-benzamide



To a solution of (3R,4R)-3-{[(3-benzyloxy-4-methoxy-benzoyl)-isopropyl-amino]-methyl}-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (0.191 g, 0.285 mmol) in dioxane (2 mL), 4N HCl in dioxane (1.07 mL) is added, and the resulting solution is stirred for 2 h, then lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 570.2 $[M+H]^+$; t_R (HPLC, C18 column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.60 min.

The starting material is prepared as follows:

A. (3S,4R)-3-Hydroxymethyl-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared under F in Example 9, Scheme 5) (19.5 g, 47.4 mmol) in MeCN (250 ml) is added Et_4NF (14.4 g, 94.8 mmol) and the resulting is refluxed for 3 h. The solvent is concentrated under reduced pressure and the crude material is taken up in AcOEt, a saturated aqueous solution of $NaHCO_3$ is added and the layers are separated. The aqueous layer is back extracted twice with AcOEt and the combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The compound was used in the next step without further purification. TLC, R_f ($MeOH/CH_2Cl_2$ 1:9): 0.22. MS (LC-MS): 273.0 $[M+H]^+$.

B. (3S,4S)-3-Hydroxymethyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-hydroxymethyl-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (13.6 g, 47.4 mmol) in dioxane (200 ml) are added Et_3N (6.64 ml, 47.4 mmol) and 1-[(2-trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione (12.3 g, 47.4 mmol). The mixture is stirred overnight at RT under nitrogen. The solvent is concentrated under reduced pressure and the crude material is taken up in AcOEt, a saturated aqueous solution of $NaHCO_3$ is added and the layers are separated. The aqueous layer is back extracted twice with AcOEt and the combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude residue is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 95:5) to afford the title compound as a yellow oil. TLC, R_f ($MeOH/CH_2Cl_2$ 2:8): 0.65. MS (LC-MS): 417.0 $[M+H]^+$.

C. (3S,4S)-3-Formyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

To a well stirred mixture of (3S,4S)-3-hydroxymethyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (16.6 g, 39.8 mmol) and Dess-Martin periodinane (16.9 g, 39.8 mmol) in CH_2Cl_2 (110 mL), slowly wet CH_2Cl_2 (0.79 mL of water in 110 mL of CH_2Cl_2) is added. The clear solution becomes cloudy toward the end of wet CH_2Cl_2 addition and is further stirred overnight. Then concentrated to a few mL of solvent by rotary evaporation and taken up in Et_2O. A solution of 1:1 10% $Na_2S_2O_3$ saturated aqueous $NaHCO_3$ is added. The layers are separated and the organic

extract is washed successively with H_2O and brine. The aqueous washings are back-extracted with Et_2O, and this organic layer is washed with H_2O and brine. The combined organic layers are dried with Na_2SO_4, filtered and concentrated. The crude mixture is used in the next step without further purification. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.48. MS (LC-MS): 437.0 $[M+Na]^+$.

D. (3R,4S)-3-Cyclopropylaminomethyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4S)-3-formyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (8.1 g, 19.5 mmol) and cyclopropylamine (1.54 mL, 21.5 mmol) in 1,2-dichloroethane (200 mL) is added $NaBH(OAc)_3$ (6.1 g, 27.3 mmol) and the mixture is stirred overnight. Then diluted with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The aqueous layer is back extracted twice with CH_2Cl_2 and the combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is used in the next step without further purification. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.45. MS (LC-MS): 456.2 $[M+H]^+$.

E. (3R,4S)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of phenylacetic acid (1.45 g, 10.53 mmol) and (3R,4S)-3-cyclopropylaminomethyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (3.2 g, 7.022 mmol) in CH_2Cl_2 (10 mL), are added triethylamine (1.47 mL, 10.53 mmol) and 1-hydroxy-7-azabenzotriazol hydrate (1.46 g, 10.53 mmol) followed 15 min later by N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (3.06 g, 15.78 mmol). The resulting mixture is stirred for 2 days at RT, then diluted with CH_2Cl_2 and poured into an aqueous 2M HCl solution. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are neutralized with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by flash chromatography on silica gel (eluent: hexane/AcOEt 2:1). TLC, R_f (hexane/AcOEt 1:1) = 0.42. MS (LC-MS): 574.2 $[M+H]^+$; t_R (HPLC, C18 column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 6.49 min.

F. (3R,4R)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

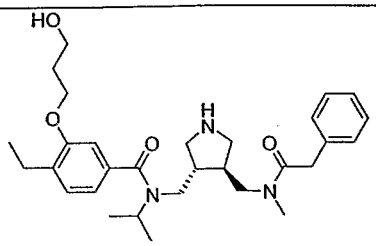
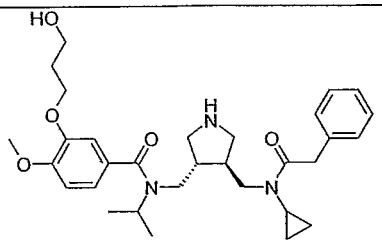
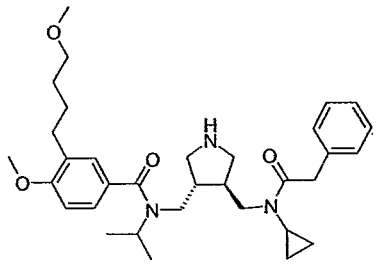
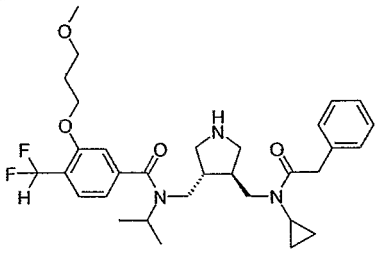
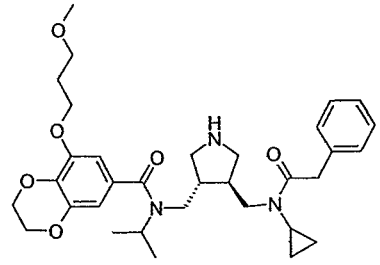
To a solution of (3R,4S)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (2.55 g, 4.44 mmol) in CH_3CN (30 mL) is added tetrabutylammonium fluoride trihydrate (4.34 g, 13.33 mmol) under a nitrogen atmosphere. The reaction mixture is stirred overnight at reflux. The solvent is removed under vacuum and Water and CH_2Cl_2 are added, the layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried (Na_2SO_4), and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:1) to give the title product. TLC, R_f (CH_2Cl_2/MeOH/NH_4OH 98:2:1) = 0.11. MS (LC-MS): 430.2 $[M+H]^+$; t_R (HPLC, C18 column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.90 min.

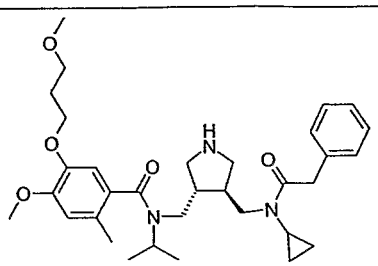
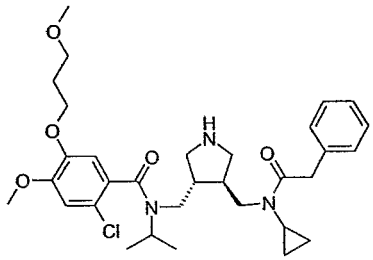
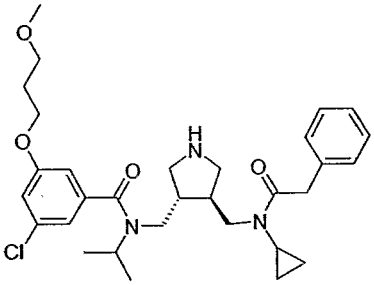
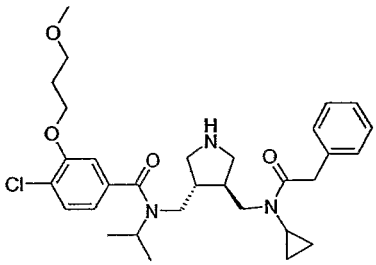
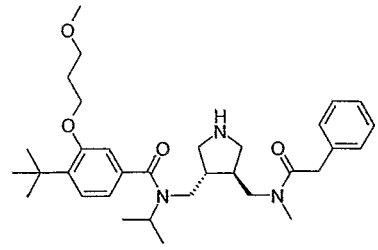
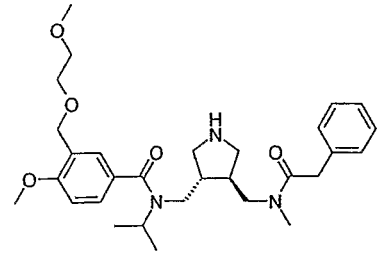
G. (3R,4R)-3-{[(3-Benzyloxy-4-methoxy-benzoyl)-isopropyl-amino]-methyl}-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

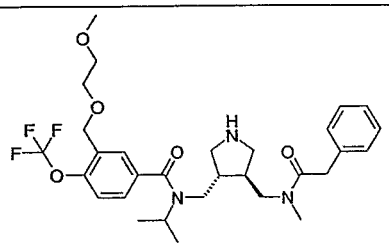
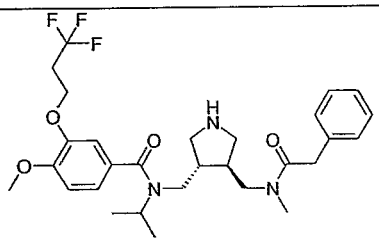
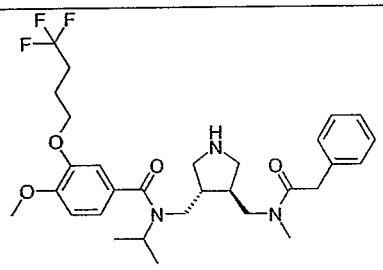
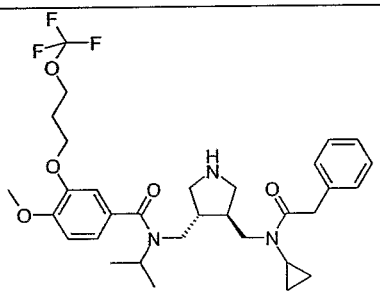
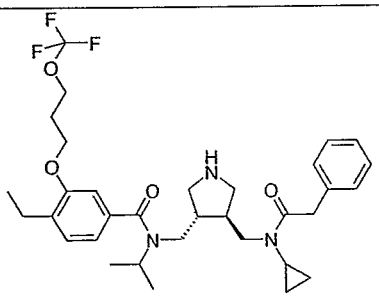
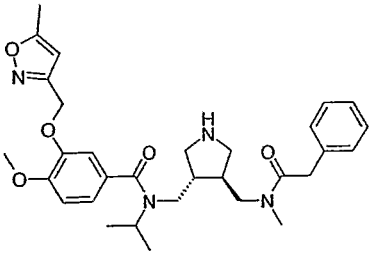
To a solution of 3-benzyloxy-4-methoxy-benzoic acid (0.19 g, 0.734 mmol) and (3R,4R)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.3 g, 0.489 mmol) in CH_2Cl_2 (10 mL), are added triethylamine (0.102 mL, 0.734 mmol) and 1-hydroxy-7-azabenzotriazol hydrate (0.102 g, 0.734 mmol) followed 15 min later by N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (0.142 g, 0.734 mmol). The resulting mixture is stirred for 2 days at RT, then diluted with CH_2Cl_2 and poured into an aqueous 2M HCl solution. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are neutralized with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by preparative HPLC. MS (LC-MS): 670.2 $[M+H]^+$; t_R (HPLC, C18 column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.76 min.

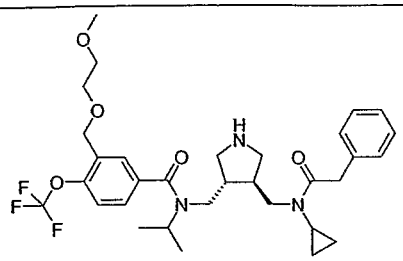
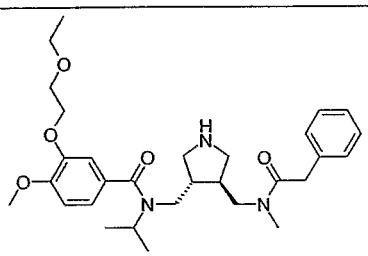
The following Examples are prepared according to the procedures as described above for Example 341, by starting from (3R,4R)-3-[(benzyl-cyclopropyl-amino)-methyl]-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (or its racemate) and the corresponding substituted benzoic acid.

Table 18:

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
342	(3S, 4S)		510.4	4.63[a]
343	(3S,4S)		538.2	3.47[c]
344	(3S*, 4S*)		550.2	4.66[c]
345	(3S*, 4S*)		572.2	4.71[c]
346	(3S*, 4S*)		580.2	4.14[c]

347	(3S*, 4S*)		566.2	4.23[c]
348	(3S*, 4S*)		586.2	4.46[c]
349	(3S*, 4S*)		556.2	4.79[c]
350	(3S*, 4S*)		556.2	4.86[c]
351	(3S,4S)		552.4	5.56[b]
352	(3S,4S)		526.2	3.66[c]

353	(3S,4S)		580.2	4.88[b]
354	(3S,4S)		550.2	4.06[c]
355	(3S,4S)		564.2	4.30[c]
356	(3S,4S)		606.2	4.63[c]
357	(3S,4S)		604.2	5.30[b]
358	(3S,4S)		549.2	4.48[b]

359	(3S,4S)		606.2	5.07[a]
360	(3S,4S)		526.2	4.40[a]

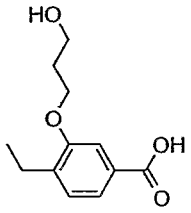
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[c] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

The following intermediates are prepared:

4-Ethyl-3-(3-hydroxy-propoxy)-benzoic acid



a. 4-Ethyl-3-hydroxy-benzoic acid

To a solution of 4-ethyl-3-(3-methoxy-propoxy)-benzoic acid (6.44 g, 27.03 mmol) in CH_2Cl_2 (150 mL) at -78°C is slowly added BBr_3 (9 mL, 93.41 mmol). The reaction mixture is allowed to reach RT and stirred for 3 hours, then poured into ice/water and filtrated to afford the title product as a white solid. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.2.

b. 4-Ethyl-3-hydroxy-benzoic acid methyl ester

To a solution of 4-ethyl-3-hydroxy-benzoic acid (3.76 g, 22.6 mmol) in MeOH (70 mL), cc H_2SO_4 (0.7 mL) is added. The solution is refluxed overnight, then concentrated to about 30 mL and poured into water. The aqueous layer is extracted with ether (50 mL x 4) and the combined organic extracts are neutralized with a saturated aqueous solution of $NaHCO_3$ (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound as a white powder. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.7, MS (LC-MS): 179.2 $[M-H]^-$, t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.8 min, flow: 1 ml/min): 4.86 min.

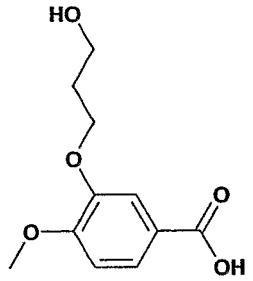
c. 4-Ethyl-3-(3-hydroxy-propoxy)-benzoic acid methyl ester

To a solution of 4-ethyl-3-hydroxy-benzoic acid methyl ester (3.21 g, 17.81 mmol) in acetonitrile (35 mL) are added 3-bromo-1-propanol (1.85 mL, 21.37 mmol) and K_2CO_3 (3.69 g, 26.7 mmol). The solution is refluxed for 4 h, then poured into water and extracted three times with AcOEt. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated to give the title product. TLC, R_f (c-hexane/AcOEt 8:2) = 0.15, MS (LC-MS): 239.2 $[M+H]^+$, t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 5.10 min.

d. 4-Ethyl-3-(3-hydroxy-propoxy)-benzoic acid

A solution of 4-ethyl-3-(3-hydroxy-propoxy)-benzoic acid methyl ester (4.68 g, 19.63 mmol) in MeOH (90 mL) and H_2O (5 mL) is treated with NaOH (2.35 g, 58.89 mmol). and heated at reflux for 5 h. The reaction mixture is extracted with AcOEt and the aqueous layer is acidified with HCl 4N and extracted three times with CH_2Cl_2. The combined organic extracts are dried over Na2SO4, filtered and concentrated in vacuo to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1, MS (LC-MS): 223.1 $[M-H]^-$, t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 4.47 min.

3-(3-Hydroxy-propoxy)-4-methoxy-benzoic acid



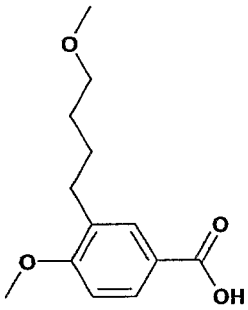
a. 3-(3-Hydroxy-propoxy)-4-methoxy-benzoic acid methyl ester

A mixture of methyl 3-hydroxy-4-methoxybenzoate (4.94 g, 26.6 mmol), 3-bromo-1-propanol (2.86 mL, 31.9 mmol) and anhydrous K_2CO_3 (5.51 g, 39.9 mmol) in MeCN (50 mL) is refluxed with stirring overnight, and after cooling is poured into ice/water. The aqueous layer is extracted with AcOEt, and the combined organics are washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (hexane/AcOEt 1:2) gives a solid residue which is stirred in a 9:1 mixture of hexane/AcOEt over 30 min. Filtration of the suspension and drying in vacuo gives the title compound as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.09. MS: 241.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 2.86 min. ^{1}H-NMR ($CDCl_3$): δ 2.13 (m, 2H), 2.59 (m, 1H), 3.92 (s, 3H), 3.93 (s, 3H), 4.29 (m, 2H), 6.92 (m, 1H), 7.60 (s, 1H), 7.73 (m, 1H) ppm.

b. 3-(3-Hydroxy-propoxy)-4-methoxy-benzoic acid

A solution of 3-(3-hydroxy-propoxy)-4-methoxy-benzoic acid methyl ester (1.00 g, 4.16 mmol) in THF (3.0 mL) and 2N NaOH (3.1 mL) is stirred at room temperature over 6 hrs. The mixture is adjusted to pH 1 by addition of 2N aqueous HCl to afford a white suspension. The precipitate is filtered, washed with water and dried in vacuo at 50 °C to give the title compound as white solid. MS: 225.0 $[M-H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.88 (m, 2H), 3.57 (m, 2H), 3.83 (s, 3H), 4.07 (m, 2H), 4.56 (s, br, 1H), 7.06 (dd, 1H), 7.46 (d, 1H), 7.57 (dd, 1H), 12.7 (s, br, 1H) ppm.

4-Methoxy-3-(4-methoxy-butyl)-benzoic acid



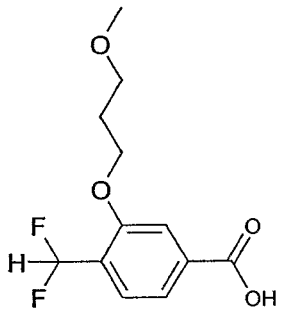
a. 4-Methoxy-3-(4-methoxy-butyl)-benzaldehyde

To a solution of 4-bromo-1-methoxy-2-(4-methoxy-butyl)-benzene (8.10 g, 29.7 mmol; described in EP0678 503 B1) in absolute THF (170 mL), cooled to -78 °C, is added dropwise over 30 min and under an argon atmosphere a 1.6M solution of n-butyllithium in hexane (20.4 mL, 32.6 mmol). After stirring for 5 min, a mixture of DMF (5.03 mL, 65.2 mmol) in THF (20 mL) is added over 30 min at -78 °C. Stirring is continued over 15 min at -78 °C, and the reaction mixture is gradually warmed and stirred for an additional hour at room temperature before quenching with 1N HCl. The aqueous layer is extracted with diethyl ether (3x 200 mL), the combined organics are dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (hexane/AcOEt 4:1) gives the title compound as yellowish oil. TLC, R_f (hexane/AcOEt 4:1) = 0.27. MS: 223.2 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.6-1.74 (m, 4H), 2.70 (t, 2H), 3.37 (s, 3H), 3.43 (t, 2H), 3.96 (s, 3H), 6.99 (dd, 1H), 7.73 (d, 1H), 7.76 (dd, 1H), 9.70 (s, 1H) ppm.

b. 4-Methoxy-3-(4-methoxy-butyl)-benzoic acid

To a stirred suspension of 4-methoxy-3-(4-methoxy-butyl)-benzaldehyde (300 mg, 1.35 mmol) and sulfamic acid (176 mg, 1.81 mmol) in 80% acetic acid (2.3 mL) is added dropwise a solution of 80% $NaClO_2$ (127 mg, 1.40 mmol; dissolved in 170 µL of H_2O) in water (0.65 mL) over 5 min and by keeping the temperature at 18-20 °C. Stirring of the yellow slurry is continued over 3 hrs at 20 °C before adding another aliquot of 80% $NaClO_2$ (151 mg, 1.67 mmol; dissolved in 205 µL of H_2O), dissolved in water (0.8 mL), and sulfamic acid (130 mg, 1.34 mmol) in 80 % aqueous acetic acid. After stirring overnight, the reaction mixture is diluted by adding water (2.3 mL), the resulting suspension is stirred for 30 min and filtered. The precipitate is dried to give the title product as white solid. TLC, R_f (CH_2Cl_2/MeOH 98:2) = 0.5. MS: 239.0 $[M+H]^+$. ^{1}H-NMR (CD_3OD): δ 1.55-1.7 (m, 4H), 2.65 (t, 2H), 3.31 (s, 3H), 3.41 (t, 2H), 3.89 (s, 3H), 4.87 (s, 1H + D_2O), 6.98 (m, 1H), 7.78 (s, 1H), 7.87 (m, 1H) ppm.

4-Difluoromethyl-3-(3-methoxy-propoxy)-benzoic acid



a. 4-Methyl-benzenesulfinic acid 3-methoxy-propyl ester

Toluene-4-sulfonyl chloride (25.4 g, 133.2 mmol) is slowly added to a solution of 3-methoxy-1-propanol (8.49 mL, 88.8 mmol) and triethylamine (14.8 mL, 106.5 mmol) in CH_2Cl_2 (80 mL) at 0°C. The reaction mixture is then allowed to warm to RT and stirred for another 16 h. The solvent is evaporated, water is added and the mixture is extracted with CH_2Cl_2. Drying (Na_2SO_4) of the combined organic extracts, filtering and evaporation of the solvent affords the crude product which is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 5:1) to give the desired product. MS (LC-MS): 262.1 $[M+18]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.12 min.

b. 4-Formyl-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester

A mixture of 4-formyl-3-hydroxybenzoic acid (1.5 g, 8.8 mmol), 4-methyl-benzenesulfinic acid 3-methoxy-propyl ester (4.5 g, 18.4 mmol), diisopropylethylamine (3.4 mL, 19.3 mmol) and NaI (2.63 g, 17.5 mmol) in DMF (20 mL) is stirred at 80°C for 60 h and at 130°C for another 5 h. The solvent is partially removed under reduced pressure, water is added and the mixture is extracted with ethyl acetate. Washing (brine) and drying (Na_2SO_4) of the combined organic extracts, filtration and evaporation of the solvent affords the crude product. The desired product is obtained by flash chromatography on silica gel (eluent: c-hexane/AcOEt 3:1). MS (LC-MS): 311.1 $[M+H]^+$; t_R (Zorbax SB C18 column, 10-95% CH_3CN/H_2O/0.8 min, 95% CH_3CN/H_2O, 0.7 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 1.20 min.

c. 4-Difluoromethyl-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester

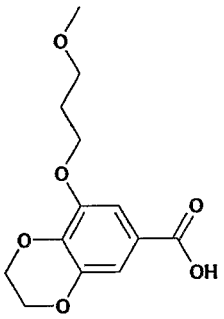
DEOXO-FLUOR (2.8 mL, 15.0 mmol) is slowly added to a solution of 4-formyl-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester (1.81 g, 5.8 mmol) in CH_2Cl_2 (15 mL) at 0°C

under Ar. The reaction mixture is then stirred at RT for 4.5 h, recooled to 0°C before ethanol (7 mL) is added. The mixture is then stirred at RT for another 16 h. The solvent is removed under reduced pressure and the crude product is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 3:1) to afford the title compound. MS (LC-MS): 333.1 $[M+H]^+$; t_R (Zorbax SB C18 column, 10-95% CH_3CN/H_2O/0.8 min, 95% CH_3CN/H_2O, 0.7 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 1.26 min

d. 4-Difluoromethyl-3-(3-methoxy-propoxy)-benzoic acid

1N aqueous KOH (6.7 mL, 6.7 mmol) is slowly added to a solution of 4-difluoromethyl-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester (1.48 g, 4.45 mmol) in MeOH (5 mL) and the reaction mixture is stirred at RT for 60 h. For workup the mixture is concentrated under reduced pressure, the residue is taken up in 2N HCl (until a pH = 1 is obtained) and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), filtered and the solvent is evaporated to give the title compound. MS (LC-MS): 259.1 $[M-H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.89 min

8-(3-Methoxy-propoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid



a. 8-Hydroxy-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester

To a solution of 3,4,5-trihydroxy-benzoic acid ethyl ester (5.00 g, 24.2 mmol) in DMF (70 mL) are added 1,2-dibromoethane (2.13 mL, 24.2 mmol) and $CsCO_3$ (16.9 g, 50.9 mmol) and the mixture is stirred overnight at room temperature and for 5 hrs at 60 °C. Extractive work-up with diethyl ether, washing of the organic phase with brine and evaporation gives the crude product as brown oil which is purified by silica gel chromatography (hexane/AcOEt 3:2). The title compound is obtained as a white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.27. MS: 223.0 $[M-H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.40 (t, 3H), 4.3-4.42 (m, 6H), 5.45 (s, 1H), 7.23 (s, 1H), 7.29 (s, 1H) ppm.

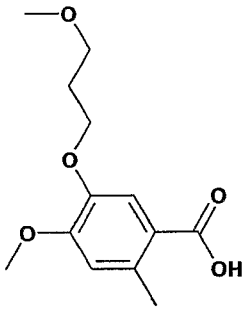
b. 8-(3-Methoxy-propoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester

The mixture of 8-hydroxy-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester (1.65 g, 7.36 mmol), 1-bromo-3-methoxypropane (1.38 g, 8.83 mmol) and anhydrous K_2CO_3 (1.53 g, 11.0 mmol) in acetone (40 mL) is refluxed overnight. After cooling to room temperature, the mixture is poured into ice water and extracted with AcOEt. The organic layer is washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (hexane/AcOEt 3:1) yields the title compound as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.32. MS: 297.0 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.41 (t, 3H), 2.16 (m, 2H), 3.40 (s, 3H), 3.61 (m, 2H), 4.20 (m, 2H), 4.31 (m, 2H), 4.35-4.45 (m, 4H), 7.27 (d, 1H), 7.31 (d, 1H) ppm.

c. 8-(3-Methoxy-propoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid

The mixture of 8-hydroxy-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester (1.85 g, 6.24 mmol) in dioxane (10 mL) and 2N NaOH (5.0 mL) is stirred at 60 °C over 1 h, then cooled to room temperature and acidified (pH 1) with 2N HCl. Volatiles are removed under reduced pressure to afford a suspension. The precipitate is filtered, washed with ice-water and dried in vacuo overnight to give the title product as white solid. TLC, R_f (hexane/AcOEt 2:1 + 1% AcOH) = 0.07. MS: 267.0 $[M-H]^+$. ^{1}H-NMR (DMSO-d_6): δ 1.96 (m, 2H), 3.26 (s, 3H), 3.48 (m, 2H), 4.05 (m, 2H), 4.27 (m, 2H), 4.31 (m, 2H), 7.07 (d, 1H9, 7.11 (d, 1H), 12.8 (s, br, 1H) ppm.

4-Methoxy-5-(3-methoxy-propoxy)-2-methyl-benzoic acid



a. 2-Methoxy-1-(3-methoxy-propoxy)-4-methyl-benzene

A stirred solution of 2-methoxy-4-methylphenol (5.00 g, 36.2 mmol), 1-bromo-3-methoxypropane (7.06 g, 45.2 mmol) and anhydrous K_2CO_3 (7.50 g, 64.3 mmol) is refluxed overnight. After cooling, volatiles are removed under reduced pressure, the residue is taken up in water and extracted with AcOEt. The combined organics are washed with brine, dried

(Na_2SO_4) and concentrated. After silica gel chromatography (hexane/AcOEt 3:1) the title compound is obtained as colorless liquid. TLC, R_f (hexane/AcOEt 2:1) = 0.34. MS: 211.0 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 2.13 (m, 2H), 2.33 (s, 3H), 3.38 (s, 3H), 3.61 (m, 2H), 3.88 (s, 3H), 4.12 (m, 2H), 6.7-6.85 (m, 3H) ppm.

b. 1-Bromo-4-methoxy-5-(3-methoxy-propoxy)-2-methyl-benzene

To a solution of 2-methoxy-1-(3-methoxy-propoxy)-4-methyl-benzene (2.00 g, 9.51 mmol) in MeCN (30 mL) is added N-bromosuccinimide (1.96 g, 10.5 mmol) at room temperature. Stirring is continued for 2 hrs, followed by evaporation of the solvent. The title compound is obtained after flash chromatography on silica gel (hexane/AcOEt 6:1) as an oil. MS: 289.0/291.0 $[M]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.04 min. ^{1}H-NMR ($CDCl_3$): δ 2.13 (m, 2H), 2.36 (s, 3H), 3.39 (s, 3H), 3.58 (m, 2H), 3.87 (s, 3H), 4.12 (m, 2H), 6.77 (s, 1H), 7.08 (s, 1H) ppm.

c. 4-Methoxy-5-(3-methoxy-propoxy)-2-methyl-benzaldehyde

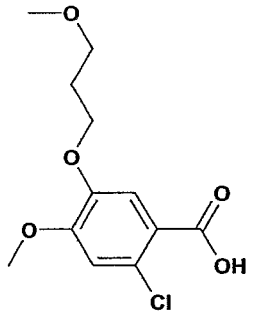
To a solution of 1-bromo-4-methoxy-5-(3-methoxy-propoxy)-2-methyl-benzene (2.50 g, 8.65 mmol) in THF (25 mL), cooled to -70 °C, is added a 1.6M solution of n-buthyllithium in hexane (5.94 mL, 9.51 mmol). After 30 min, DMF (1.05 mL, 13.0 mmol) is added and stirring is continued overnight while the reaction mixture is gradually warmed to room temperature. Quenching with ice-cold 1N aqueous HCl is followed by extraction with diethyl ether. The combined organic layers are washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (hexane/AcOEt 7:2) gives the title compound as oil. TLC, R_f (hexane/AcOEt 1:1) = 0.29. MS: 239.2 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 2.16 (m, 2H), 2.66 (s, 3H), 3.39 (s, 3H), 3.60 (m, 2H), 3.97 (s, 3H), 4.18 (m, 2H), 6.73 (s, 1H), 7.40 (s, 1H), 10.2 (s, 1H) ppm.

d. 4-Methoxy-5-(3-methoxy-propoxy)-2-methyl-benzoic acid

To a solution of 4-methoxy-5-(3-methoxy-propoxy)-2-methyl-benzaldehyde (1.25 g, 5.25 mmol) in a 3:1 mixture of tert-butanol/CH_2Cl_2 (60 mL) is added 2-methyl-2-butene (25.0 mL), followed by dropwise addition of a solution of $NaClO_2$ (5.81 g, 51.4 mmol) and NaH_2PO_4 (4.07 g, 33.6 mmol) in water (45 mL) over 15 min at room temperature, and stirring is continued overnight. The reaction mixture is poured into ice/saturated aqueous $NaHCO_3$ solution, the water phase is washed with AcOEt, then acidified and extracted with AcOEt.

The combined organics are washed with brine, dried (Na_2SO_4) and concentrated to give a yellow solid. The crude product is stirred for 30 min in a 95:5 mixture of hexane/diisopropyl ether (25 mL), the precipitate is filtered off, washed with a 95:5 mixture of hexane/diisopropyl ether and dried to give the title compound as yellowish solid. MS: 253.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.23 min. ^{1}H-NMR ($CDCl_3$): δ 1.96 (m, 2H), 2.51 (s, 3H), 3.27 (s, 3H), 3.48 (m, 2H), 3.84 (s, 3H), 4.00 (m, 2H), 6.89 (s, 1H), 7.41 (s, 1H) ppm.

2-Chloro-4-methoxy-5-(3-methoxy-propoxy)-benzoic acid



a. 2-Chloro-5-hydroxy-4-methoxy-benzaldehyde

2-Chloro-4,5-dimethoxybenzaldehyde (5.00 g, 24.9 mmol; commercially available from Akos Consulting) is dissolved at room temperature in conc. H_2SO_4 (23 mL; Riedel) at room temperature. The deeply colored mixture is heated at 65 °C overnight with stirring, and after cooling is poured with caution into ice-water containing 38 g of solid NaOH (pH 14). The water phase is washed twice with AcOEt, and then is adjusted to pH 1 by addition of HCl 37% with ice-cooling to form a white suspension. Extraction with AcOEt, drying of the organics over $MgSO_4$ and evaporation gives the crude product in a mixture with unreacted starting material. The title compound is obtained after silica gel chromatography (hexane/AcOEt gradient from 3:1 to 1:1) as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.35. MS: 187.0 $[M+H]^+$. $]^+$. ^{1}H-NMR (DMSO-d_6): δ 3.41 (s, 3H), 7.14 (s, 1H), 7.45 (s, 1H), 9.83 (s, 1H), 10.2 (s, 1H) ppm.

b. 2-Chloro-4-methoxy-5-(3-methoxy-propoxy)-benzaldehyde

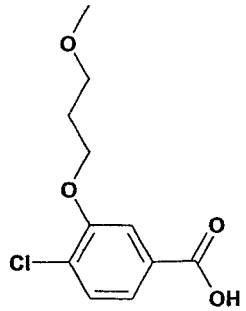
A mixture of crude 2-chloro-5-hydroxy-4-methoxy-benzaldehyde (1.79 g, 8.15 mmol), 1-bromo-3-methoxypropane (1.53 g, 9.79 mmol) and anhydrous K_2CO_3 (1.69 g, 12.2 mmol) in MeCN (30 mL) is refluxed overnight. Ice water is added to the mixture, followed by extraction with AcOEt. The combined organics are washed with brine, dried (Na_2SO_4) and

concentrated. The title compound is obtained after purification by RP-HPLC on a PrepC_{18} OBD column (dimensions: 30x100 mm; 5 µM particle size, SunFire Ltd), and using a 95-5% gradient of MeCN/H_2O 5:95 (containing 0.1% TFA) to MeCN/H_2O 95:5 (containing 0.1% TFA) over 20 min, as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.42. MS: 259.0 $[M+H]^+$. $]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.15 min. ^{1}H-NMR ($CDCl_3$): δ 2.15 (m, 2H), 3.39 (s, 3H), 3.59 (m, 2H), 3.99 (s, 3H), 4.19 (m, 2H), 6.91 (s, 1H), 7.45 (s, 1H), 10.4 (s, 1H) ppm.

c. 2-Chloro-4-methoxy-5-(3-methoxy-propoxy)-benzoic acid

To a solution of 2-chloro-4-methoxy-5-(3-methoxy-propoxy)-benzaldehyde (1.08 g, 3.55 mmol) in a 3:1 mixture of tert-butanol/CH_2Cl_2 (20 mL) is added 2-methyl-2-butene (0.74 g, 5.32 mmol), followed by dropwise addition of a solution of $NaClO_2$ (0.67g, 7.10 mmol) and NaH_2PO_4 (0.67 g, 4.26 mmol) in water (14 mL) over 15 min at room temperature, and stirring is continued overnight. The reaction mixture is poured into ice/saturated aqueous $NaHCO_3$ solution, the water phase is washed with AcOEt. The ice-cold aqueous layer is acidified with HCl 37% to form a white precipitate which is filtered off, washed with ice-cold water and dried in vacuo. The compound is obtained as white solid. MS: 273.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.25 min. ^{1}H-NMR ($CDCl_3$): δ 1.96 (m, 2H), 3.25 (s, 3H), 3.47 (m, 2H), 3.85 (s, 3H), 4.03 (m, 2H), 7.10 (s, 1H), 7.39 (s, 1H) ppm.

4-Chloro-3-(3-methoxy-propoxy)-benzoic acid



a. 4-Chloro-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester

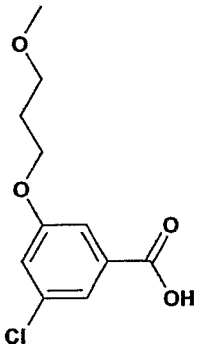
A mixture of 4-chloro-3-hydroxy-benzoic acid (4.02 g, 23.3 mmol; commercially available from Frinton Laboratories), 1-bromo-3-methoxypropane (8.73 g, 55.9 mmol) and anhydrous K_2CO_3 (9.66 g, 69.9 mmol) in MeCN (80 mL) is refluxed overnight. A further amount of 1-

bromo-3-methoxypropane (1.82 g, 0.5 equiv.) is added under reflux conditions. After 2 hrs, the mixture is poured into ice-water and extracted with AcOEt. The combined organics are washed with brine, dried (Na_2SO_4) and concentrated. Flash-chromatography on silica gel (hexane/AcOEt 7:2) affords the title compound as an oil. TLC, R_f (hexane/AcOEt 3:1) = 0.17. MS: 317.2 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.13 min. ^{1}H-NMR ($CDCl_3$): δ 2.08 (m, 2H), 2.16 (m, 2H), 3.40 (s, 6H), 3.57 (m, 2H), 3.65 (m, 2H), 4.23 (m, 2H), 4.45 (m, 2H), 7.45 (m, 1H), 7.61 (m, 1H), 7.64 (s, 1H) ppm.

b. 4-Chloro-3-(3-methoxy-propoxy)-benzoic acid

A solution of 4-chloro-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester (1.58 g, 4.99 mmol) in aqueous 2N NaOH (3.23 mL, 6.48mmol) and dioxane (10 mL) is stirred at room temperature for 3.5 hrs. The mixture is acidified by addition of 2N HCl, the volatiles are removed by evaporation and the obtained suspension is filtered. The precipitate is washed with ice-cold water and dried in vacuo to give the title compound as white solid. MS: 243.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.93 min. ^{1}H-NMR (DMSO-d_6): δ 2.00 (m, 2H), 3.27 (s, 3H), 3.34 (s, br, 1H), 3.53 (m, 2H), 4.19 (m, 2H), 7.5-7.6 (m, 3H) ppm.

3-Chloro-5-(3-methoxy-propoxy)-benzoic acid



a. 3-Chloro-5-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester

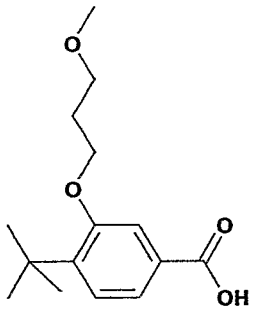
The title compound is obtained from 3-chloro-5-hydroxy-benzoic acid (1.96 g, 11.4 mmol; commercially available from J&W Pharm Lab), 1-bromo-3-methoxypropane (4.25 g, 27.3 mmol) and anhydrous K_2CO_3 (4.71 g, 34.1 mmol), as described above for the 4-chloro regioisomer, as oil. TLC, R_f (hexane/AcOEt 3:1) = 0.21. MS: 317.0 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$):

δ 2.07 (m, 2H), 2.10 (m, 2H), 3.39 (s, 3H), 3.41 (s, 3H), 3.56 (m, 2H), 3.59, (m, 2H), 4.13 (m, 2H), 4.45 (m, 2H), 7.13 (m, 1H), 7.49 (m, 1H), 7.63 (m, 1H) ppm.

b. 3-Chloro-5-(3-methoxy-propoxy)-benzoic acid

The title compound is obtained from 3-chloro-5-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester (1.70 g, 5.37 mmol), dissolved in dioxane (10 mL), by hydrolysis with 2N aqueous NaOH as a white solid. MS: 243.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.04 min. ^{1}H-NMR (DMSO-d_6): δ 1.96 (m, 2H), 3.25 (s, 3H), 3.36 (s, br, 1H), 3.48 (m, 2H), 4.11 (m, 2H), 7.31 (s, 1H), 7.40 (s, 1H), 7.49 (s, 1H) ppm.

4-tert-Butyl-3-(3-methoxy-propoxy)-benzoic acid



a. 4-tert-Butyl-3-methoxy-benzoic acid methyl ester

To a solution of 4-tert-butyl-3-methoxy-benzoic acid (3.00 g, 14.4 mmol; commercially available from Apin, 41226B) in MeOH (30 mL) is added H_2SO_4 conc. (3 mL) and the mixture is refluxed for 5 hrs. After cooling, the mixture is diluted with water, extracted twice with diethyl ether, the combined organics are dried (Na_2SO_4) and evaporated to dryness to give the title compound as yellowish oil. MS: 223.0 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 6.12 min. ^{1}H-NMR ($CDCl_3$): δ 1.41 (s, 9H), 3.91 (s, 3H), 3.92 (s, 3H), 7.36 (dd, 1H), 7.54 (d, 1H), 7.60 (dd, 1H) ppm.

b. 4-tert-Butyl-3-hydroxy-benzoic acid methyl ester

To a solution of borontribromide (3.38 mL, 35.1 mmol) in CH_2Cl_2 (35 mL), cooled to -60 °C, is added under an argon atmosphere a solution of 4-tert-butyl-3-methoxy-benzoic acid methyl ester (2.60 g, 11.7 mmol) in CH_2Cl_2 (65 mL). The reaction is warmed to room temperature and stirring is continued overnight. Another aliquot of BBr_3 (1.13 mL, 11.7

mmol) is added, and the mixture is stirred for 6 hrs at ambient temperature before quenching by careful addition of water. The aqueous layer is extracted with CH_2Cl_2, the combined organics are washed with 1N aqueous NaOH, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (eluents: CH_2Cl_2 100%, then CH_2Cl_2/acetone 97:3) gives the title compound as yellowish solid. MS: 209.0 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.37 min. ^{1}H-NMR ($CDCl_3$): δ 1.46 (s, 9H), 3.94 (s, 3H), 5.60 (s, 1H), 7.36 (dd, 1H), 7.50 (d, 1H), 7.57 (dd, 1H) ppm.

The alkaline aqueous layers obtained above are acidified with HCl conc., extracted with CH_2Cl_2, the organics are dried (Na_2SO_4) and evaporated to dryness to give 4-tert-butyl-3-hydroxy-benzoic acid: MS: 193.0 $[M+H]^+$. ^{1}H-NMR (DMSO-d_6): δ 1.37 (s, 9H), 7.26 (m, 1H), 7.33 (m, 1H), 7.40 (m, 1H), 9.71 (s, 1H), 12.7 (s, 1H) ppm.

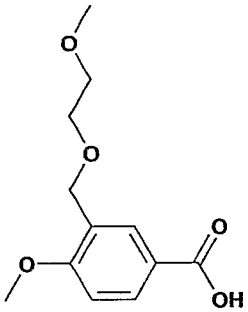
c. 4-tert-Butyl-3-(3-methoxy-propoxy)-benzoic acid methyl ester

A mixture of 4-tert-butyl-3-hydroxy-benzoic acid methyl ester (1.56 g, 7.49 mmol), 3-bromopropyl methyl ether (1.72 g, 11.2 mmol) and anhydrous K_2CO_3 (1.55 g, 11.2 mmol) in MeCN (30 mL) is refluxed overnight. After cooling, the mixture is filtered, the filtrate is diluted with CH_2Cl_2 and the organics are washed with aqueous 0.5M NaOH, aqueous 0.5M HCl and water, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (hexane/AcOEt 97:3) gives the title compound as colorless oil. MS: 281.1 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 6.22 min. ^{1}H-NMR ($CDCl_3$): δ 1.43 (s, 9H), 2.17 (m, 2H), 3.41 (s, 3H), 3.65 (m, 2H), 3.93 (s, 3H), 4.18 (m, 2H), 7.36 (dd, 1H), 7.96 (d, 1H), 7.60 (dd, 1H) ppm.

d. 4-tert-Butyl-3-(3-methoxy-propoxy)-benzoic acid

The title compound is obtained by hydrolysis of 4-tert-butyl-3-(3-methoxy-propoxy)-benzoic acid methyl ester (1.60 g, 5.14 mmol), dissolved in EtOH (15 mL), in the presence of aqueous 2N NaOH (3.85 mL, 7.70 mmol) as off-white powder. MS: 284.1 $[M+H_2O]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.42. ^{1}H-NMR (DMSO-d_6): δ 1.36 (s, 9H), 2.04 (m, 2H), 3.26 (s, 3H), 3.94 (m, 2H), 4.09 (m, 2H), 7.34 (m, 1H), 7.49 (s, 1H), 7.48 (m, 1H), 12.8 (s, br, 1H) ppm.

4-Methoxy-3-(2-methoxy-ethoxymethyl)-benzoic acid



a. (5-Bromo-2-methoxy-phenyl)-methanol

To a suspension of 5-bromo-2-methoxy-benzaldehyde (7.00 g, 32.2 mmol) in MeOH (40 mL), cooled to 0 to 5 °C, is added $NaBH_4$ (1.40 g, 35.4 mmol). After stirring for 1 h, the mixture is poured into ice-water, followed by extraction with AcOEt. The combined organics are washed with brine, dried (Na_2SO_4) and concentrated to give the title product as off-white solid. TLC, R_f (hexane/AcOEt 3:1) = 0.19. ^{1}H-NMR ($CDCl_3$): δ 2.24 (m, 2H), 3.88 (s, 3H), 4.68 (d, 2H), 6.79 (dd, 1H), 7.41 (dd, 1H), 7.45 (d, 1H) ppm.

b. 4-Bromo-1-methoxy-2-(2-methoxy-ethoxymethyl)-benzene

To a solution of (5-bromo-2-methoxy-phenyl)-methanol (3.38 g, 14.8 mmol) and 2-bromoethyl methyl ether (2.06 g, 14.8 mmol) in DMF (30 mL) is added NaH (55% dispersion in oil; 1.36 g, 31.1 mmol) in three portions at room temperature, followed by stirring overnight. The mixture is poured into ice-cooled aqueous 2N HCl, the water phase is extracted with diethyl ether, the combined organic phase is washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (hexane/AcOEt 3:1) gives the title compound as liquid. TLC, R_f (hexane/AcOEt 1:1) = 0.44. ^{1}H-NMR ($CDCl_3$): δ 3.45 (s, 3H), 3.64 (m, 2H), 3.71 (m, 2H), 3.83 (s, 3H), 4.60 (s, 2H), 6.76 (d, 1H), 7.37 (dd, 1H), 7.56 (d, 1H) ppm.

c. 4-Methoxy-3-(2-methoxy-ethoxymethyl)-benzoic acid ethyl ester

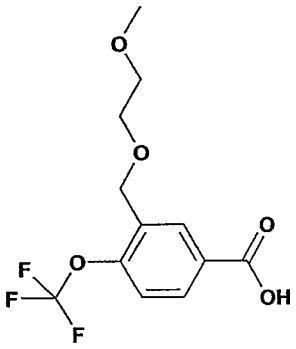
To a solution of 4-bromo-1-methoxy-2-(2-methoxy-ethoxymethyl)-benzene (2.88 g, 10.5 mmol) in absolute THF (30 mL) is added at -70 °C a 1.6N solution of n-butyllithium in hexane (7.20 mL, 11.5 mmol) with stirring. After 40 min, ethyl chloroformate (1.14 g, 10.5 mmol) is added, and the mixture is stirred overnight while gradually warming up to room temperature. The mixture is poured into 2N aqueous HCl, extracted with CH_2Cl_2, the organic layers are dried (Na_2SO_4) and concentrated. The crude product is purified by flash chromatography on

silica gel (hexane/AcOEt 2:1) to give the title compound as liquid. TLC, R_f (hexane/AcOEt 1:1) = 0.13.

d. 4-Methoxy-3-(2-methoxy-ethoxymethyl)-benzoic acid

A solution of 4-methoxy-3-(2-methoxy-ethoxymethyl)-benzoic acid ethyl ester (0.87 g, 3.24 mmol) in a 1:1 mixture of THF and 4N NaOH (10 mL) is stirred at 50 °C overnight. After cooling, the volatiles are removed at reduced pressure, the remaining aqueous phase is acidified to pH 1 by dropwise addition of HCl 37%, and the resulting suspension is filtered off. The precipitate is washed with water, dried overnight in vacuo to give the title compound. TLC, R_f (hexane/AcOEt 1:1) = 0.07. MS: 239.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 2.71 min. ^{1}H-NMR (DMSO-d_6): δ 3.29 (s, 3H), 3.52 (m, 2H), 3.64 (m, 2H), 3.88 (s, 3H), 4.51 (s, 2H), 7.10 (m, 1H), 7.90 (m, 1H), 7.94 (m, 1H), 12.6 (s, br, 1H) ppm.

3-(2-Methoxy-ethoxymethyl)-4-trifluoromethoxy-benzoic acid



a. (5-Bromo-2-trifluoromethoxy-phenyl)-methanol

To a solution of 5-bromo-2-trifluoromethoxy-benzoic acid (2.00 g, 7.02 mmol, commercially available from Rare Chemicals, AL BE 0523) and NEt_3 (1.47 mL, 10.5 mmol) in THF (50 mL), cooled to -15 °C and under an argon atmosphere, is added dropwise isobutylchloroformate (1.15 mL, 8.77 mmol). The mixture is stirred for 1 hr after warming to room temperature, followed by addition of AcOEt (20 mL). The organic layer is subsequently washed with 0.5M HCl (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL) and water (20 mL), then dried over Na_2SO_4 and concentrated to give the mixed anhydride intermediate.

To a solution of the mixed anhydride obtained above (1.50 g, 3.90 mmol) in THF (40 mL), cooled to 0-5 °C, is added dropwise a solution of $LiBH_4$ (0.17 g, 7.79 mmol) in THF (5mL). After warming to room temperature, the reaction mixture is stirred overnight and then quenched by adding aqueous 2N NaOH (30 mL). Extraction of the water phase with AcOEt,

drying of the combined organics (Na_2SO_4) and evaporation to dryness gives the title compound as white powder. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.04 min. ^{1}H-NMR (DMSO-d_6): δ 4.56 (d, 2H), 5.51 (t, 1H), 7.31 (dd, 1H), 7.59 (dd, 1H), 7.73 (d, 1H) ppm.

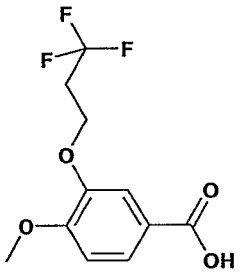
b. 4-Bromo-2-(2-methoxy-ethoxymethyl)-1-trifluoromethoxy-benzene

In a 3-neck flask under argon, a 55-65% dispersion of NaH in oil (0.097 g, 2.44 mmol) is washed with n-pentane, the organics are removed and DMF (10 mL) is added. The mixture is cooled to 0-5 °C, and a solution of (5-bromo-2-trifluoromethoxy-phenyl)-methanol (0.60 g, 2.21 mmol) in DMF (3.0 mL) is added dropwise. After warming to room temperature, stirring is continued for 1 h before this mixture is added to a solution of 2-bromoethyl methyl ether (0.312 mL, 3.32 mmol) in DMF (3mL). After 4 hrs at room temperature, the reaction is still incomplete by TLC. Another aliquot of NaH (1 equiv; oil dispersion washed with pentane) and 2-bromoethyl methyl ether (0.312 mL, 3.32 mmol) are added, followed by stirring for 18 hrs at room temperature. The mixture is poured into ice-water and extracted with AcOEt, the combined organics are dried (Na_2SO_4) and evaporated to dryness to give the title compound as yellowish oil. MS: 346.0/348.0 $[M+H_2O]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.80 min. ^{1}H-NMR ($CDCl_3$): δ 3.49 (s, 3H), 3.64 (m, 2H), 3.72 (m, 2H), 4.69 (s, 2H), 7.13 (dd, 1H), 7.46 (dd, 1H), 7.77 (d, 1H) ppm.

c. 3-(2-Methoxy-ethoxymethyl)-4-trifluoromethoxy-benzoic acid

To a solution of 4-bromo-2-(2-methoxy-ethoxymethyl)-1-trifluoromethoxy-benzene (0.28 g, 0.85 mmol) in absolute diethyl ether (2.0 mL), cooled to -70 °C, is dropwise added under an argon atmosphere a 1.7M solution of tert.-butyllithium in pentane (0.50 mL, 0.85 mmol). After stirring for 30 min, CO_2 gas is bubbled into the solution for 2 min followed by stirring the yellow solution at -70 °C for additional 30 min. The reaction is quenched by addition of a saturated aqueous NH_4Cl solution (2 mL). The basic aqueous layer is washed with AcOEt and, after acidification to pH 1, is extracted twice with AcOEt. The combined organics are dried over Na_2SO_4 and evaporated to dryness to give the title compound as colorless oil. MS: 293.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.62 min. ^{1}H-NMR ($CDCl_3$): δ 3.46 (s, 3H), 3.67 (m, 2H), 3.76 (m, 2H), 4.71 (s, 2H), 7.35 (dd, 1H), 8.09 (dd, 1H), 8.35 (dd, 1H) ppm.

4-Methoxy-3-(3,3,3-trifluoro-propoxy)-benzoic acid



a. 4-Methoxy-3-(3,3,3-trifluoro-propoxy)-benzoic acid ethyl ester

The mixture of 3-hydroxy-4-methoxy-benzoic acid ethyl ester (1.75 g, 8.92 mmol), methanesulfonic acid 3,3,3-trifluoro-propyl ester (2.06 g, 10.7 mmol) and anhydrous K_2CO_3 (2.49 g, 17.8 mmol) in acetone (20 mL) is heated with stirring at reflux temperature overnight. After cooling, the mixture is diluted with AcOEt followed by washing of the organic phase with 2N aqueous NaOH and brine. The organic layer is dried over Na_2SO_4 and evaporated, and the crude product is purified by silica gel chromatography (eluent: hexane/AcOEt 5:1) to give the title compound as oil. TLC, R_f (hexane/AcOEt 1:1) = 0.59. MS: 293.0 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.42 (t, 3H), 2.74 (m, 2H), 3.96 (s, 3H), 4.33 (m, 2H), 4.40 (m, 2H), 6.94 (m, 1H), 7.59 (s, 1H), 7.77 (m, 1H) ppm.

b. 4-Methoxy-3-(3,3,3-trifluoro-propoxy)-benzoic acid

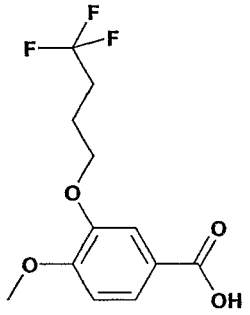
The title compound is obtained as white solid from 4-methoxy-3-(3,3,3-trifluoro-propoxy)-benzoic acid ethyl ester (0.62 g, 2.12 mmol), dissolved in THF (3.0 mL), after hydrolysis in the presence of 2N NaOH (1.6 mL) at 60 °C overnight. The ice-cold reaction mixture is acidified (pH 1) with HCl 37 % to form a white precipitate which is filtered off, washed with water and dried in vacuo. TLC, R_f (hexane/AcOEt 1:1) = 0.17. MS: 263.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.50 min. ^{1}H-NMR ($CDCl_3$): δ 2..81 (m, 2H), 3.85 (s, 3H), 4.25 (m, 2H), 7.10 (dd, 1H), 7.49 (d, 1H), 7.63 (dd, 1H), 12.6 (s, br, 1H) ppm.

The methanesulfonic acid 3,3,3-trifluoro-propyl ester is prepared according to the following procedure:

To the mixture of 3,3,3-trifluoro-1-propanol (1.28 g, 10.8 mmol) and NEt_3 (4.53 mL, 32.7 mmol) in CH_2Cl_2 (10 mL) is added dropwise at -20 °C methanesulfochloride (1.03 mL, 13.1 mmol). The mixture is slowly warmed over 90 min to 5 °C with stirring, followed by addition of CH_2Cl_2 and washing of the organic layer with 2N aqueous HCl. The organics are dried over

Na_2SO_4 and concentrated in vacuo to give the crude title product as yellowish liquid which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 2.64 (m, 2H), 3.09 (s, 3H), 4.47 (t, 2H) ppm.

4-Methoxy-3-(4,4,4-trifluoro-butoxy)-benzoic acid



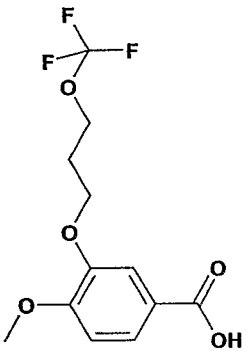
a. 4-Methoxy-3-(4,4,4-trifluoro-butoxy)-benzoic acid ethyl ester

A suspension of 3-hydroxy-4-methoxy-benzoic acid ethyl ester (1.00 g, 5.10 mmol), 1-bromo-4,4,4-trifluorobutane (1.12 g, 5.86 mmol) and anhydrous K_2CO_3 (2.14 g, 15.3 mmol) in MeCN (10 mL) is refluxed with stirring overnight. After cooling, the mixture is filtered, and the filtrates are evaporated to drying to give the title compound as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.62. MS: 307.0 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.42 (m, 3H), 2.1-2.2 (m, 2H), 2.3-2.45 (m, 2H), 3.95 (s, 3H), 4.14 (m, 2H), 4.39 (m, 2H), 6.93 (dd, 1H), 7.58 (d, 1H), 7.74 (dd, 1H) ppm.

b. 4-Methoxy-3-(4,4,4-trifluoro-butoxy)-benzoic acid

A mixture of 4-methoxy-3-(4,4,4-trifluoro-butoxy)-benzoic acid ethyl ester (0.93 g, 3.04 mmol) in THF (3 mL) and 2N NaOH (2.28 mL, 4.55 mmol) is heated with stirring at 60 °C overnight. After cooling, ice water is added and the pH is adjusted to 1 by addition of HCl 37% to form a white precipitate which is filtered off. The title compound is obtained after drying as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.17. MS: 277.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.90 min. ^{1}H-NMR ($CDCl_3$): δ 1.98 (m, 2H), 2.45 (m, 2H), 3.85 (s, 3H), 4.08 (m, 2H), 7.08 (dd, 1H), 7.46 (d, 1H), 7.60 (dd, 1H), 12.7 (s, br, 1H) ppm.

4-Methoxy-3-(3-trifluoromethoxy-propoxy)-benzoic acid



a. Dithiocarbonic acid *O*-(3-ethoxy-propyl) ester *S*-methyl ester

The title compound is prepared by the method described in Bull. Chem. Soc. Jpn. (2000), 73, 477f.: To a cooled solution of 3-ethoxy-1-propanol (24.4 g, 0.227 mol) in DMF (150 mL) is added NaH (60% dispersion in oil; 10.0 g, 0.250 mol) in portions over 1 hour, keeping the reaction temperature below 5 °C. Stirring is continued for 5 hrs at room temperature, the mixture is cooled to 5 to 10 °C followed by dropwise addition of CS_2 (27.5 mL, 0.454 mol). The mixture is gradually warmed to ambient temperature overnight and then cooled to <10 °C before adding iodomethane (17.9 mL, 0.284 mol). Stirring is continued for 18 hrs at room temperature, the mixture is then poured into ice-cold diluted aqueous HCl and extracted with diethyl ether. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated to give a yellow oil. Purification by flash chromatography on silica gel (hexane/AcOEt 20:1) gives the title compound as yellow liquid. TLC, R_f (hexane/AcOEt 3:1) = 0.56. ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H), 2.11 (m, 2H), 2.60 (s, 3H), 3.52 (t, 2H), 3.58 (t, 2H), 4.79 (t, 2H) ppm.

b. 1-Ethoxy-3-trifluoromethoxy-propane

Following the method described in Tetrahedron Letters (1992), 33, 4173-4176, a suspension of 1,3-dibromo-5,5-dimethylhydantoin (78.5 g, 0.266 mol) in CH_2Cl_2 (0.8 L) is cooled to -70 °C, followed by dropwise addition of hydrogen fluoride/pyridine (99.2 mL, 3.82 mol; Fluka No 47586). To this mixture is then slowly added a solution of dithiocarbonic acid *O*-(3-ethoxy-propyl) ester *S*-methyl ester (23.0 g, 0.089 mol) in CH_2Cl_2 (200 mL). The yellow reaction mixture is warmed to ambient temperature over 3.5 hrs and then quenched by addition of an ice-cold aqueous solution of $NaHSO_3$/$NaHCO_3$/NaOH until the red-brownish color of the mixture disappears. The aqueous phase is adjusted to pH >10 by addition of solid sodium hydroxide with stirring, the organic phase is separated, washed with brine and filtered. Removal of the solvent (CH_2Cl_2) is achieved by distillation at atmospheric pressure (<35 °C boiling temperature). Fractions boiling between 37 °C and 110 °C are combined, taken up in

CH_2Cl_2 (100 mL) and washed with 2N aqueous HCl. The aqueous layer is re-extracted with CH_2Cl_2 (40 mL), the combined organics are dried (Na_2SO_4) and filtered. The solvent is removed in a distillation apparatus at normal pressure (oil bath at 50 °C) to obtain the title compound as a pale yellow liquid. ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H), 1.98 (m, 2H), 3.48-3.57 (m, 4H), 4.12 (t, 2H) ppm. ^{19}F-NMR ($CDCl_3$): δ -60.8 ppm.

c. Trifluoro-methanesulfonic acid 3-trifluoromethoxy-propyl ester

Following a similar procedure as described in J. Org. Chem. (2001), 66, 1061-1063, 1-ethoxy-3-trifluoromethoxy-propane (1.50 g, 6.10 mmol) is added to a mixture of trifluoromethanesulfonic anhydride (4.04 mL, 23.8 mmol) and trifluoromethanesulfonic acid (0.15 mL, 1.65 mmol) with stirring. The mixture is heated at 60 °C overnight, cooled to room temperature and poured into ice-water. The aqueous layer is extracted with CH_2Cl_2, the combined organics are dried over Na_2SO_4 and filtered. Volatiles are removed by distillation at normal pressure (bath temperature at 65 °C) to give a mixture of trifluoro-methanesulfonic acid ethyl ester and the title compound as pale yellow liquid (used without further purification). ^{1}H-NMR ($CDCl_3$): δ 2.25 (m, 2H), 4.16 (m, 2H), 4.70 (m, 2H) ppm.

d. 4-Bromo-1-methoxy-2-(3-trifluoromethoxy-propoxy)-benzene

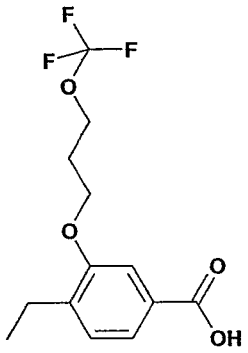
A mixture of 5-bromo-2-methoxy-phenol (1.20 g, 5.62 mmol), crude trifluoro-methanesulfonic acid 3-trifluoromethoxy-propyl ester (2.52 g, 6.74 mmol; purity of 74%) and anhydrous K_2CO_3 (1.18 g, 8.42 mmol) in MeCN (8 mL) is stirred in a sealed flask at room temperature overnight and then filtered. The combined filtrates are concentrated and the crude product is chromatographed over silica gel (eluent: toluene) to give the title compound as oil. TLC, R_f (toluene/AcOEt 10:1) = 0.63. ^{1}H-NMR ($CDCl_3$): δ 2.25 (m, 2H), 3.87 (s, 3H), 4.13 (m, 2H), 4.23 (m, 2H), 6.79 (dd, 1H), 7.04 (d, 1H), 7.09 (dd, 1H) ppm. ^{19}F-NMR ($CDCl_3$): δ -60.7 ppm.

e. 4-Methoxy-3-(3-trifluoromethoxy-propoxy)-benzoic acid

To a solution of 4-bromo-1-methoxy-2-(3-trifluoromethoxy-propoxy)-benzene (1.11 g, 3.20 mmol) in THF (10 mL), cooled to -60 to -70 °C, is added dropwise a 1.6M solution of n-butyllithium in hexane (2.30 mL, 3.69 mmol). After stirring for 30 min, a stream of CO_2 gas is bubbled into the yellow solution for 10 min. The reaction is quenched by adding 2N aqueous HCl and volatiles are removed by evaporation. The water phase is alkalized by addition of 4N NaOH, washed with AcOEt and then acidified with HCl 37% to form a white suspension. Extraction with CH_2Cl_2, drying of the organics over Na_2SO_4 and evaporation gives the title product as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.09. MS: 293.0 $[M-H]^+$. t_R (HPLC,

Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.00 min. ^{1}H-NMR ($CDCl_3$): δ 2.15 (m, 2H), 3.85 (s, 3H), 4.10 (m, 2H), 4.27 (m, 2H), 7.08 (dd, 1H), 7.48 (d, 1H), 7.60 (dd, 1H) ppm. ^{19}F-NMR (DMSO-d_6): δ -58.2 ppm.

4-Ethyl-3-(3-trifluoromethoxy-propoxy)-benzoic acid



a. 4-Ethyl-3-(3-trifluoromethoxy-propoxy)-benzoic acid methyl ester

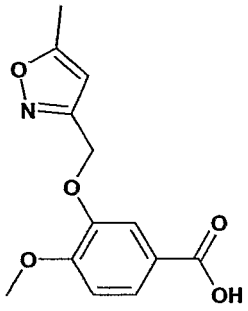
A mixture of 4-ethyl-3-hydroxy-benzoic acid methyl ester (250 mg, 1.32 mmol), crude trifluoro-methanesulfonic acid 3-trifluoromethoxy-propyl ester (590 mg, 1.58 mmol; purity of 74%) and anhydrous K_2CO_3 (276 mg, 1.98 mmol) in MeCN (2.0 mL) is stirred in a sealed glas vial overnight at room temperature. The crude product obtained after filtration and evaporation is purified by flash chromatography (hexane/AcOEt 1:1) to give the title compound as oil. TLC, R_f (hexane/AcOEt 3:1) = 0.38. ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, 3H), 2.25 (m, 2H), 2.70 (q, 2H), 3.94 (s, 3H), 4.18 (t, 2H), 4.24 (t, 2H), 7.25 (d, 1H), 7.52 (s, 1H), 7.64 (d, 1H) ppm. ^{19}F-NMR ($CDCl_3$): δ -61.1 ppm.

b. 4-Ethyl-3-(3-trifluoromethoxy-propoxy)-benzoic acid

The title compound is obtained from 4-ethyl-3-(3-trifluoromethoxy-propoxy)-benzoic acid methyl ester (155 mg, 0.506 mmol) by hydrolysis in THF (3 mL) in the presence of aqueous 2N NaOH (0.38 mL, 0.76 mmol) at 60 °C overnight. After cooling to room temperature, volatiles are removed in vacuo and the residue is portioned between 2N aqueous HCl and CH_2Cl_2. The combined organics are dried (Na_2SO_4) and evaporated to dryness to give the title compound as a white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.17. MS: 291.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.99 min. ^{1}H-NMR (DMSO-d_6): δ 1.15 (t,

3H), 2.18 (m, 2H), 2.64 (q, 2H), 4.13 (t, 2H), 4.29 (t, 2H), 7.28 (d, 1H), 7.45 (s, 1H), 7.51 (d, 1H), 12.65 (s, br, 1H) ppm. ^{19}F-NMR (DMSO-d_6): δ -59.1 ppm.

4-Methoxy-3-(5-methyl-isoxazol-3-ylmethoxy)-benzoic acid



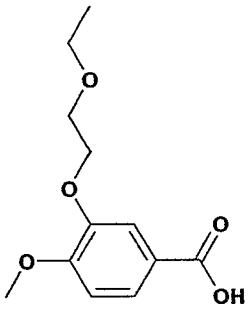
a. 4-Methoxy-3-(5-methyl-isoxazol-3-ylmethoxy)-benzoic acid ethyl ester

A mixture of 3-hydroxy-4-methoxy-benzoic acid (2.00 g, 10.2 mmol), 3-(chloromethyl)-5-methylisoxazole (1.61 g, 12.2 mmol; commercially available from Maybridge, SPB01262DA), anhydrous K_2CO_3 (2.11 g, 15.3 mmol) and NaI (0.31 g, 2.04 mmol) in MeCN (35 mL) is refluxed overnight. After cooling to room temperature, the mixture is filtered, the filtrate is diluted with CH_2Cl_2 and the organics are washed with aqueous 0.5M NaOH, water and brine. Drying over Na_2SO_4 and evaporation to dryness affords the crude title compound as oil. MS: 292.0 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.14 min. ^{1}H-NMR ($CDCl_3$): δ 1.39 (t, 3H), 2.45 (s, 3H), 3.93 (s, 3H), 4.35 (q, 2H), 5.20 (s, 2H), 6.15 (s, 1H), 6.15 (dd, 1H), 6.90 (d, 1H), 7.70 (dd, 1H) ppm.

b. 4-Methoxy-3-(5-methyl-isoxazol-3-ylmethoxy)-benzoic acid

The title compound is obtained by hydrolysis of 4-methoxy-3-(5-methyl-isoxazol-3-ylmethoxy)-benzoic acid ethyl ester (2.90 g, 8.96 mmol), dissolved in EtOH (25 mL), in the presence of 2N NaOH (6.72 mL, 13.4 mmol) at 70 °C for 3 hrs. After cooling to room temperature, volatiles are removed in vacuo, the aqueous phase is washed with CH_2Cl_2 and then acidified to pH 1 by addition of conc. HCl. The precipitate is filtered off and dried to give an off-white powder. MS: 264.0 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.98 min. ^{1}H-NMR (DMSO-d_6): δ 2.39 (s, 3H), 3.82 (s, 3H), 5.15 (s, 2H), 6.30 (s, 1H), 7.06 (dd, 1H), 7.54 (d, 1H), 7.59 (dd, 1H), 12.7 (s, br, 1H) ppm.

3-(2-Ethoxy-ethoxy)-4-methoxy-benzoic acid



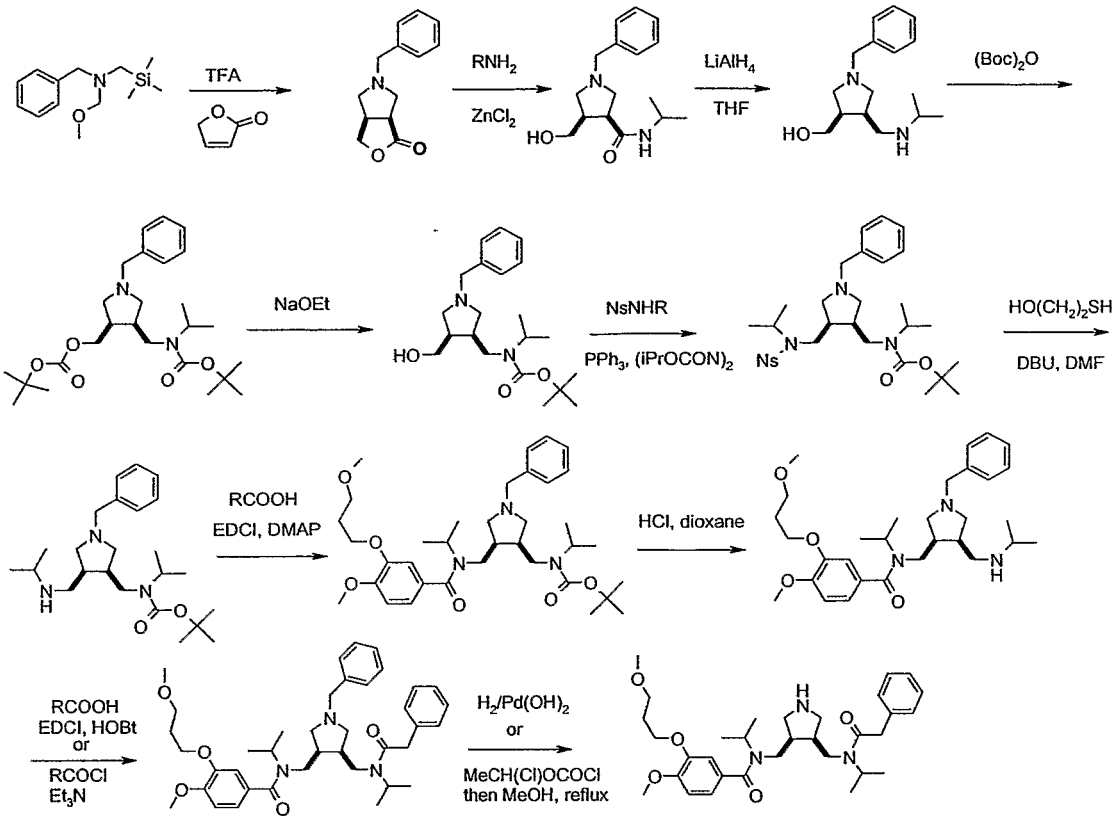
a. 3-(2-Ethoxy-ethoxy)-4-methoxy-benzoic acid ethyl ester

A mixture of 3-hydroxy-4-methoxy-benzoic acid ethyl ester (1.60 g, 8.16 mmol), 2-bromoethyl ethyl ether (1.38 mL, 12.2 mmol) and anhydrous K_2CO_3 (1.69 g, 12.2 mmol) in MeCN (35 mL) is refluxed overnight. In order to complete the reaction, an additional aliquot of 2-bromoethyl ethyl ether (1.38 mL, 12.2 mmol) and a catalytic amount of NaI are added, and reflux is continued overnight. After cooling, the mixture is filtered and the filtrates are concentrated. The residue is taken up in CH_2Cl_2, the organic layer is washed with 0.5M NaOH and water, dried (Na_2SO_4) and concentrated. The title compound is obtained after flash chromatography (hexane/AcOEt 8:2) as colorless oil. MS: 269.0 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.92 min. ^{1}H-NMR ($CDCl_3$): δ 1.27 (m, 3H), 1.41 (m, 3H), 3.64 (m, 2H), 3.87 (m, 2H), 3.94 (s, 3H), 4.26 (m, 2H), 4.38 (m, 2H), 9.91 (dd, 1H), 7.63 (d, 1H), 7.72 (dd, 1H) ppm.

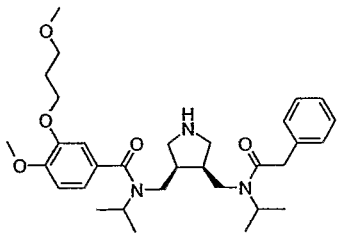
b. 3-(2-Ethoxy-ethoxy)-4-methoxy-benzoic acid

The title compound is obtained from 3-(2-ethoxy-ethoxy)-4-methoxy-benzoic acid ethyl ester (1.41 g, 5.26 mmol) by hydrolysis in EtOH (15 mL) in the presence of aqueous 2N NaOH (3.94 mL, 7.88 mmol) at 50 °C overnight as a white powder. MS: 239.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.78 min. ^{1}H-NMR (DMSO-d_6): δ 1.11 (t, 3H), 3.48 (q, 2H), 3.68 (m, 2H), 3.80 (s, 3H), 4.08 (m, 2H), 7.03 (dd, 1H), 7.43 (d, 1H), 7.55 (dd, 1H), 12.6 (s, br, 1H) ppm.

Scheme 7



Example 361: N-Isopropyl-N-{(3R*,4S*)-4-[(isopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-methoxy-3-(3-methoxy-propoxy)-benzamide



A solution of N-{(3R*,4S*)-1-benzyl-4-[(isopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide (0.15 g, 0.24 mmol) and 1-chloroethyl chloroformate (0.10 mL, 0.97 mmol) in $ClCH_2CH_2Cl$ is refluxed for 2 h under a nitrogen atmosphere, and MeOH (10 mL) is then added at room temperature. The mixture is heated for 2 h at 80°C, and concentrated to give the title product. For purification, the N-Boc protected compound, (3S*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(isopropyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester, is prepared analogously as described for the title compound D in Example 361,

Scheme 7. The crude product is purified by flash chromatography on silica gel (eluent: cHexane/AcOEt 50/50) to give the product. MS (LC-MS): 654.4 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.92 min.

The pure title compound is prepared analogously as described for the title compound under I in Example 361, Scheme 7. MS (LC-MS): 554.4 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.23 min.

A. (3aR*,6aS*)-5-Benzyl-hexahydro-furo[3,4-c]pyrrol-1-one

To a mixture of γ-crotonolactone (0.99 mL, 13.5 mmol) and N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine (5.0 g, 20.2 mmol) in CH_2Cl_2 (50 mL) is added dropwise TFA (0.10 mL, 1.30 mmol) at 0°C The reaction mixture is stirred overnight at room temperature and quenched with an aqueous saturated solution of $NaHCO_3$ (30 mL). CH_2Cl_2 is added, the layers are separated and the aqueous one back extracted twice with CH_2Cl_2. The combined organic extracts are dried over $MgSO_4$, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: AcOEt/hexane 10:90 to 20:80) to give the titled product. TLC, Rf (AcOEt/hexane 3:7) = 0.73. MS (LC-MS): 218.1 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 2.95 min.

B. (3S*,4R*)-1-Benzyl-4-hydroxymethyl-pyrrolidine-3-carboxylic acid isopropyl-amide

A suspension of (3aR*,6aS*)-5-benzyl-hexahydro-furo[3,4-c]pyrrol-1-one (1.50 g, 6.90 mmol) and $ZnCl_2$ (0.94 g, 6.90 mmol) in $iPrNH_2$ (20 mL) is refluxed overnight under a nitrogen atmosphere. The crude material is filtered over a pad of Celite and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH 70:25:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.38. MS (LC-MS): 277.2 $[M+H]^+$.

C. [(3R*,4R*)-1-Benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-yl]-methanol

To a ice-cooled solution of $LiAlH_4$ (0.56 g, 14.76 mmol) in THF (25 mL), is added dropwise a solution of (3S*,4R*)-1-benzyl-4-hydroxymethyl-pyrrolidine-3-carboxylic acid isopropylamide (1.02 g, 3.69 mmol) in THF (5 mL). The reaction mixture is refluxed overnight and quenched with $Na_2SO_4.10\ H_2O$ (4 g) at 0°C. Ether is added, the mixture is stirred for 2 h at room

temperature. The crude material is filtered over a pad of Celite and concentrated to give the title compound which is used without further purification in the next step. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.28. MS (LC-MS): 263.2 $[M+H]^+$; $]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 2.94 min.

D. Carbonic acid (3R*,4S*)-1-benzyl-4-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-pyrrolidin-3-ylmethyl ester tert-butyl ester

A suspension of [(3R*,4R*)-1-benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-yl]-methanol (1.13 g, 4.31 mmol), $NaHCO_3$ (1.45 g, 17.24 mmol), and Boc_2O (1.88 g, 8.62 mmol) in MeOH (50 mL) is stirred overnignt at room temperature. The mixture is heated for 1 h at 65°C, and then concentrated to a few mL of solvent by rotary evaporation. Water and CH_2Cl_2 are added, the layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried ($MgSO_4$), and concentrated to give the title compound which is used without further purification in the next step. TLC, R_f (AcOEt) = 0.81. MS (LC-MS): 463.3 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.08 min.

E. ((3S*,4R*)-1-Benzyl-4-hydroxymethyl-pyrrolidin-3-ylmethyl)-isopropyl-carbamic acid tert-butyl ester

A mixture of carbonic acid (3R*,4S*)-1-benzyl-4-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-pyrrolidin-3-ylmethyl ester tert-butyl ester (2.02 g, 4.31 mmol) and NaOEt (0.59 g, 8.62 mmol) in EtOH (35 mL) is stirred for 2 h at room temperature. The solvent is concentrated and the residue is diluted by CH_2Cl_2 and H_2O. The layers are separated and the organic extract is washed successively with H_2O and brine. The combined organic layers are dried with $MgSO_4$, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 95:5) to give the title product. TLC, R_f (AcOEt) = 0.23. MS (LC-MS): 363.3 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.06 min.

F. ((3S*,4R*)-1-Benzyl-4-{[isopropyl-(2-nitro-benzenesulfonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-isopropyl-carbamic acid tert-butyl ester

To a solution of ((3S*,4R*)-1-benzyl-4-hydroxymethyl-pyrrolidin-3-ylmethyl)-isopropyl-carbamic acid tert-butyl ester (0.60 g, 1.66 mmol), N-isopropyl-2-nitro-benzenesulfon-amide (0.49 g, 1.99 mmol), and PPh_3 (0.52 g, 1.99 mmol) in toluene (15 mL), is added dropwise diisopropyl azodicarboxylate (0.39 mL, 1.99 mmol) at 0°C under a nitrogen atmosphere. The solution is stirred for 1 h at room temperature, and then heated at 65°C for 1 h. The reaction mixture is concentrated. The crude material is used purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 3:7) to give the crude product. To the solid product is added a mixture of Et_2O/hexane (1:1) and the resulting suspension is filtered. The solid is washed with Et_2O/hexane (1:1) solution, and then the combined filtrate is concentrated to give a titled product. TLC, R_f (AcOEt) = 0.61. MS (LC-MS): 589.3 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.39 min.

G. [(3S*,4S*)-1-Benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-isopropyl-carbamic acid tert-butyl ester

A solution of ((3S*,4R*)-1-benzyl-4-{[isopropyl-(2-nitro-benzenesulfonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-isopropyl-carbamic acid tert-butyl ester (8.9 g, 23.02 mmol), 2-mercaptoethanol (0.81 mL, 11.60 mmol), and DBU (0.79 mL, 5.27 mmol) in CH_3CN (10 mL) is stirred for 2 h at room temperature. The mixture is concentrated and then diluted with Et_2O and H_2O. The organic layer is separated, and the aqueous phase is extracted 3 times with Et_2O. The combined organic extracts are dried ($MgSO_4$), and the solvent is concentrated to give the title compound which is used without further purification in the next step. TLC, R_f (AcOEt) = 0.61. MS (LC-MS): 404.3 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.45 min.

H. [(3S*,4R*)-1-Benzyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-isopropyl-carbamic acid tert-butyl ester

To a solution of [(3S*,4S*)-1-benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-isopropyl-carbamic acid tert-butyl ester (0.32 g, 0.55 mmol), 4-methoxy-3-(3-methoxy-propoxy)-benzoic acid (0.23 g, 0.96 mmol), DMAP (0.12 g, 0.96 mmol), and triethyl-amine (0.56 mL, 0.96 mmol) in DMF (10 mL), is added EDCI-HCl (0.19 g, 0.96 mmol) at 0°C. The reaction mixture is stirred overnight at room temperature. Water and Et_2O are added, the layers are separated and the aqueous one is extracted twice with Et_2O. The combined

organic extracts are dried ($MgSO_4$), and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 90:10) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.72. MS (LC-MS): 626.4 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.28 min.

I. N-[(3R*,4R*)-1-Benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

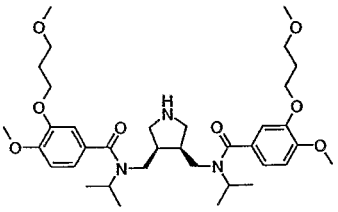
To a solution of [(3S*,4R*)-1-benzyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-isopropyl-carbamic acid tert-butyl ester (0.41g, 0.66 mmol), is added a dioxane solution of HCl 4N (10 mL). The reaction mixture is stirred for 2 h at room temperature. The solvent is concentrated and water (20 mL), an aqueous solution of NaOH 4N (5 mL) and Et_2O (25 mL) are added. The layers are separated and the aqueous one extracted twice with Et_2O. The combined organic extracts are dried ($MgSO_4$), and the solvent is removed *in vacuo* to give the title compound which is used without further purification in the next step. MS (LC-MS): 526.4 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.53 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.78 min.

J. N-{(3R*,4S*)-1-Benzyl-4-[(isopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

To a solution of N-[(3R*,4R*)-1-benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide (0.19 g, 0.36 mmol), triethyl-amine (0.15 mL, 1.09 mmol), and DMAP (0.013 g, 0.11 mmol) in CH_2Cl_2, is added dropwise phenyl-acetyl chloride (0.058 mL, 0.44 mmol) at 0°C under a nitrogen atmosphere. The solution is stirred overnight at room temperature. The mixture is added an aqueous solution of NaOH 0.1N (50 mL) and CH_2Cl_2 (50 mL). The organic layer is separated and the aqueous phase extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 90:10) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.23. MS (LC-MS): $[M+H]^+$; 644.4 t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.95 min.

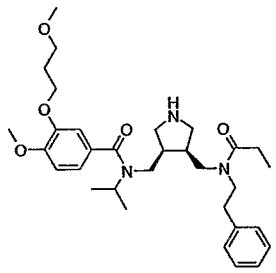
The following Examples are prepared according to the procedures described above for Example 361 :

Example 362: N-Isopropyl-N-{(3R*,4S*)-4-[(isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzoyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-methoxy-3-(3-methoxy-propoxy)-benzamide



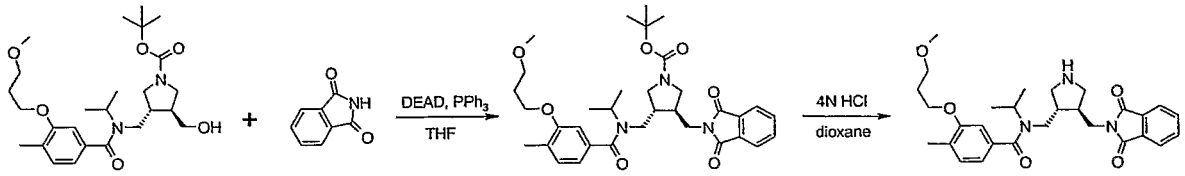
The title compound is prepared analogously as described in Example 361 by coupling N-[(3R*,4R*)-1-benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide and 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid in step J. MS (LC-MS): 658.3 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.20 min.

Example 363: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-{(3R,4S)-4-[(phenethyl-propionyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

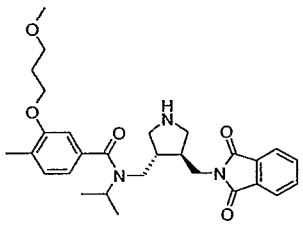


The title compound is prepared analogously as described in Example 361 using ((3S*,4R*)-1-benzyl-4-hydroxymethyl-pyrrolidin-3-ylmethyl)-isopropyl-carbamic acid tert-butyl ester and 2-nitro-N-phenethyl-benzenesulfonamide in step F, then propionyl chloride as the acylating agent in step H and 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid as acylating agent in step J. MS (LC-MS): 554.4 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.26 min.

Scheme 8



Example 364: N-[(3S,4S)-4-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide



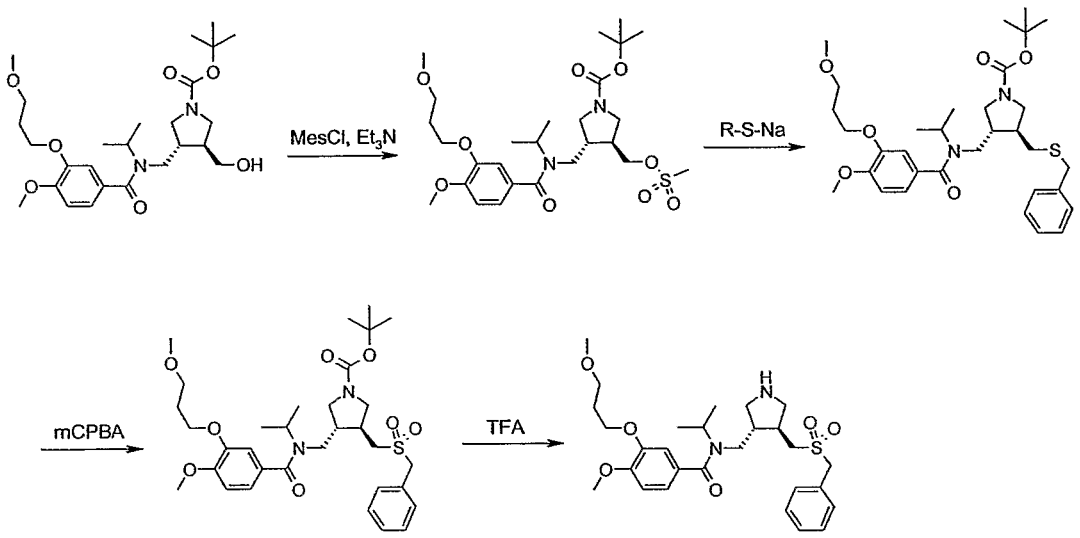
(3R,4R)-3-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (180 mg, 0.30 mmol) is dissolved 4N HCl in dioxane (5 mL) and stirred at RT for 30 min. Lyophilization affords the corresponding hydrochloride salt. MS (LC-MS): 508.1 $[M+H]^+$; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 2.58 min.

The starting material is prepared as follows:

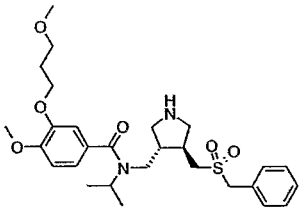
(3R,4R)-3-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

DEAD is slowly added to a solution of (3S,4R)-3-hydroxymethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (210 mg, 0.44 mmol), phthalimide (07 mg, 0.66 mmol) and PPh_3 (173 mg, 0.66 mmol) in THF (5 mL) at RT. The resulting yellow solution is stirred for another 2 h before H_2O is added and the mixture is extracted with ethyl acetate. Drying (Na_2SO_4) of the extracts, filtration and evaporation of the solvent affords the crude product which is purified by preparative HPLC (Waters C_{18} ODB, eluent: CH_3CN/H_2O 5%/2 min, CH_3CN/H_2O 5-100%/10 min, 100% CH_3CN/2.5 min, flow 20 mL/min) to give the desired product. MS (LC-MS): 630.2 $[M+Na]^+$; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.40 min.

Scheme 9:

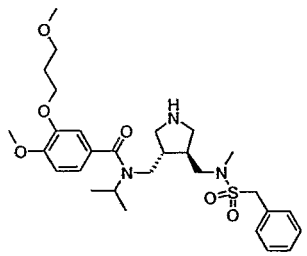


Example 365: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-((3S*,4S*)-4-phenyl-methanesulfonyl methyl-pyrrolidin-3-ylmethyl)-benzamide



The title compound is prepared as shown in Scheme 9.

Example 366: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-{(3S*,4S*)-4-[(methyl-phenylmethanesulfonyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide



To a solution of (3R*,4S*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylmethanesulfonyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-

butyl ester (49 mg, 0.074 mmol) in 2 mL CH_2Cl_2, TFA (86 µL, 1.11 mmol) is added. The mixture is stirred 4 h at RT and then poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on an Isolute SPE Flash NH_2 column (eluent: CH_2Cl_2/MeOH 100:0 to 95:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.2. MS (LC-MS): 563.0 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.55 min.

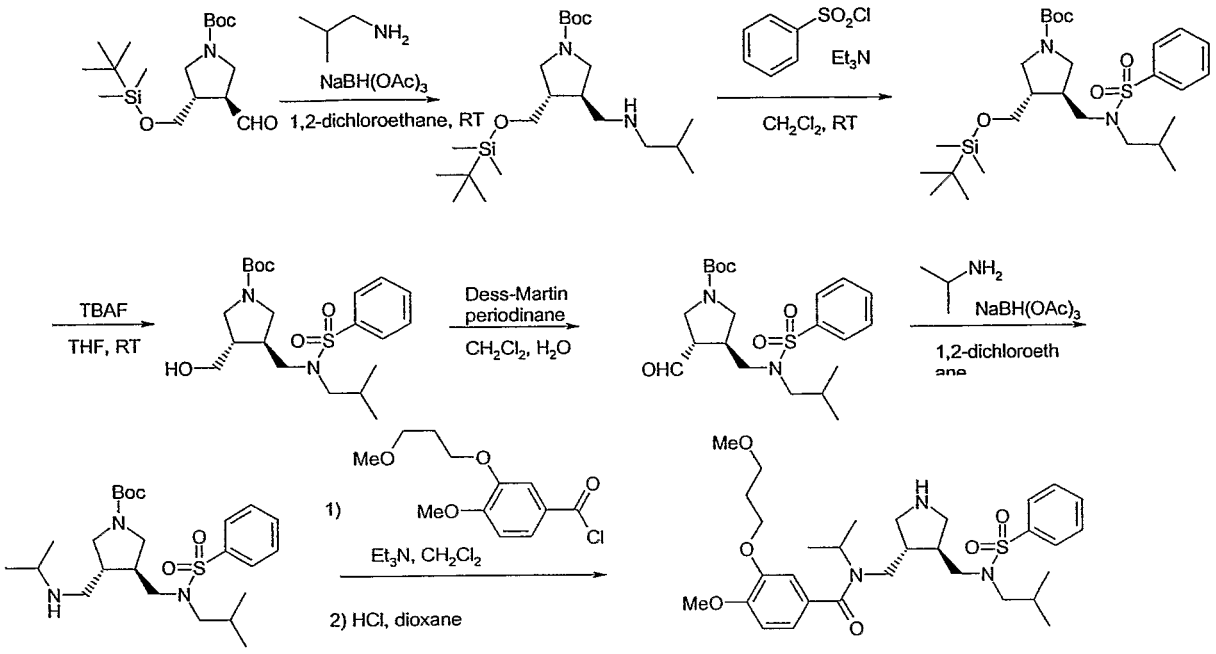
To a solution of the free base in dioxane (2 mL), 4N HCl in dioxane (0.074 mmol, 19 µL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt as a white powder.

The starting material is prepared as follows:

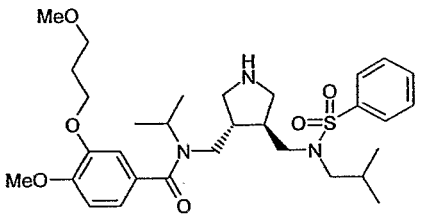
(3R*,4S*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylmethanesulfonyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (89 mg, 0.175 mmol) in CH_2Cl_2 (3 mL), alpha-toluenesulfonyl chloride (40 mg, 0.21 mmol) and triethylamine (30 µL, 0.21 mmol) are added under N_2 atmosphere. The mixture is stirred overnight at RT, diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous one is extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude product is purified by preparative HPLC (C18-ODB-AQ, 5 µm, 20x50 mm, YMC, eluent: CH_3CN /H_2O + 0.1 % HCOOH flow: 20 mL/min). The HPLC fractions are collected, and the resulting solution is lyophilized to afford the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.81 min.

Scheme 10



Example 367: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-{(3S*,4S*)-4-[(isobutyl-phenylsulfonyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide



4N HCl/dioxane (4 mL) is added to a solution of (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(isobutyl-phenylsulfonyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (0.804 g, 1.17 mmol) in dioxane (5 mL). After 3 h the solution is lyophilized to give the title compound a a colorless powder. MS (LC-MS): 590.3 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.91 min.

The starting material is prepared as follows:

A. (3S*,4R*)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-(isobutylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared as described above for Example 9 / step F (Scheme 5) from (3S*,4S*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester and isobutylamine. MS (LC-MS): 401.1 $[M+H]^+$; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 3.70 min.

B. N-[(3S*,4S*)-4-(tert-Butyl-dimethyl-silanyloxymethyl)-pyrrolidin-3-ylmethyl]-N-isobutyl-benzenesulfonamide

The title compound is prepared as described above in Example 366 / step A from (3S*,4R*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isobutylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and phenylsulfonyl chloride. TLC, R_f (CH_2Cl_2/MeOH 98:2) = 0.42; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 5.58 min.

C. N-((3S*,4S*)-4-Hydroxymethyl-pyrrolidin-3-ylmethyl)-N-isobutyl-benzenesulfonamide

The title compound is prepared as described above for Example 9 / step H (Scheme 5) from N-[(3S*,4S*)-4-(tert-butyl-dimethyl-silanyloxymethyl)-pyrrolidin-3-ylmethyl]-N-isobutyl-benzenesulfonamide. MS (LC-MS): 327.1 $[M-Boc+H]^+$; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.17 min.

D. N-((3S*,4S*)-4-Formyl-pyrrolidin-3-ylmethyl)-N-isobutyl-benzenesulfonamide

The title compound is prepared as described above for Example 9 / step E (Scheme 5) from N-((3S*,4S*)-4-Hydroxymethyl-pyrrolidin-3-ylmethyl)-N-isobutyl-benzenesulfonamide. MS (LC-MS): 325.0 $[M-Boc+H]^+$; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.24 min.

E. (3S*,4R*)-3-[(Benzenesulfonyl-isobutyl-amino)-methyl]-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared as described above for Example 9 / step F (Scheme 5) from N-((3S*,4S*)-4-formyl-pyrrolidin-3-ylmethyl)-N-isobutyl-benzenesulfonamide and isopropylamine. MS (LC-MS): 468.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18

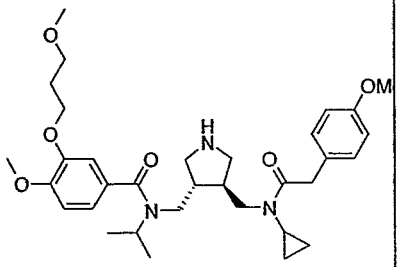
column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.94 min.

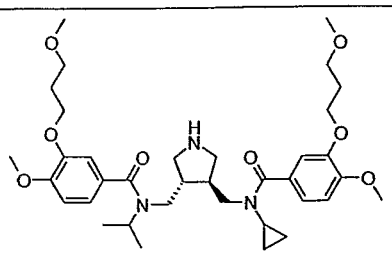
F. (3R*,4R*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(isobutyl-phenylsulfonyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

Triethylamine (0.48 mL, 3.43 mmol) followed by 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid chloride (621 mg, 2.4 mmol) (prepared from 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid and $SOCl_2$ in CH_2Cl_2) is added to a solution of (3S*,4R*)-3-[(benzenesulfonyl-isobutyl-amino)-methyl]-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.07 g, 2.3 mmol) in CH_2Cl_2 (30 mL) and stirred at RT for 16 h. For workup a sat. solution of $NaHCO_3$ is added and the mixture is extracted with ethyl acetate. The combined organic extracts are dried (Na_2SO_4), filtered and the solvent is evaporated. Purification of the crude product by flash chromatography on silica gel (eluent gradient: c-hexane/AcOEt1:1 to 3:7) yields the title compound. TLC, R_f (c-hexane/AcOEt 3:7) = 0.40; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.10 min.

The following Examples are prepared according to the procedures described above in Examples 8, 9, 10, 11, 12 and 13:

Table 19:

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
368	(3S*, 4S*)		582.4	4.51

369	(3S,4S)		656.4	4.37

Conditions RP-HPLC: column: Nucleosil C18-HD (4 x 70 mm, 3 µM); solvent A: H_2O/0.1% TFA, solvent B: MeCN/0.1% TFA; gradient: 5-100% solvent B over 6 min, then 100% solvent B over 1.5 min, then 100 to 5% solvent B over 0.5 min; flow: 1.0 mL/min.

Example 370: Soft Capsules

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of any one of the compounds of formula I mentioned in any one of the preceding Examples, are prepared as follows:

1. Composition

Active ingredient	250 g
Lauroglycol	2 liters

Preparation process: The pulverized active ingredient is suspended in Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulverizer to produce a particle size of about 1 to 3 µm. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

Example 371: Tablets comprising compounds of the formula I

Tablets, comprising, as active ingredient, 100 mg of any one of the compounds of formula I in any one of the preceding Examples are prepared with the following composition, following standard procedures:

Composition

Active Ingredient	100 mg
crystalline lactose	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg

magnesium stearate	5 mg
	447 mg

Manufacture: The active ingredient is mixed with the carrier materials and compressed by means of a tabletting machine (Korsch EKO, stamp diameter 10 mm).

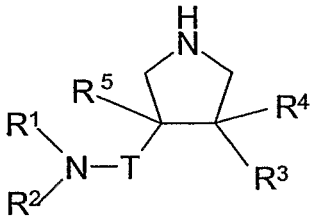
Avicel® is microcrystalline cellulose (FMC, Philadelphia, USA). PVPPXL is polyvinyl-polypyrrolidone, cross-linked (BASF, Germany). Aerosil® is silicon dioxide (Degussa, Germany).

Example 372: Renin inhibiting activity of the compounds in examples 1 to 369:

Using the test systems mentioned above, IC_{50} values for the compounds in the preceding examples 1 to 369 can be found in the range from 1 nM to 20 μM.

What is claimed is:

1. The use of a compound of the formula I,



(I)

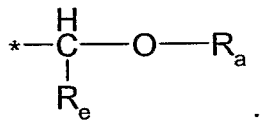
wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

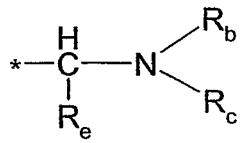
R^3 is a moiety selected from the group of moieties of the formulae

(a)

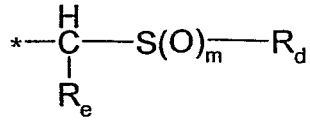


;

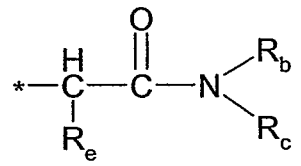
(b)



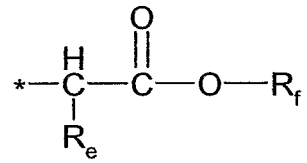
(c)



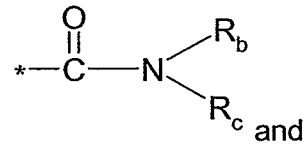
(d)



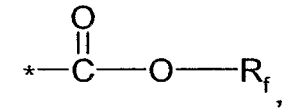
(e)



(f)

 and

(g)



where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the moieties given under R_a, with the proviso that preferably not more than one of R_b and R_c is acyl, or R_b and R_c may form together a 3 to 7 membered nitrogen containing ring which can be unsubstituted or substituted;

Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;

R_e is hydrogen, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl; and
R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;
m is 0, 1 or 2;
each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;
and T is methylene, methylene mono-substituted by alkyl, or is carbonyl or thiocarbonyl;
or a pharmaceutically acceptable salt thereof,
in the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin.

2. The use according to claim 1 of a compound of the formula I wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;
R^2 is unsubstituted or substituted mono- or bicyclic aryl-alkyl;
R^3 is a moiety selected from the group of moieties of the formulae (a), (b), (c), (d), (e), (f) or (g) given in the first description of a compound of the formula I in this disclosure;
where in any of the moieties of these moiety formulae the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,
R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the moieties given under R_a, with the proviso that preferably not more than one of R_b and R_c is acyl,

Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (preferably if m is 0) acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;

R_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl or hydrogen; and

R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;

m is 0, 1 or 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy, preferably hydrogen;

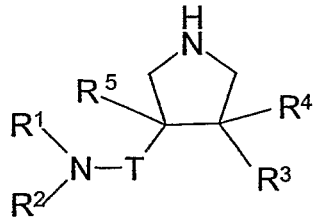
and T is methylene ($-CH_2-$), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-) , carbonyl (-C(=O)-) or thiocarbonyl (-C(=S)-);

or a pharmaceutically acceptable salt thereof,

in the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin.

3. The use according to claim 1 or according to claim 2 where the disease to be treated is hypertension.

4. A compound of the formula I,



(I)

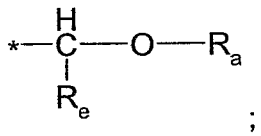
wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, substituted monocyclic or unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl; with the proviso that if R^1 is one of the moieties mentioned in the definition of R^1 other than acyl then R^2 can also be unsubstituted monocyclic aryl-alkyl;

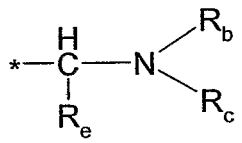
R^3 is a moiety selected from the group of moieties of the formulae

(a)

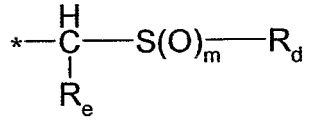


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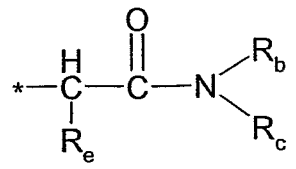
(b)



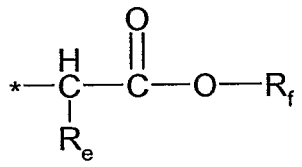
(c)



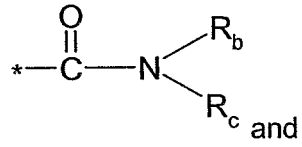
(d)



(e)

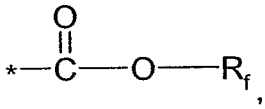


(f)



and

(g)



where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen, with the proviso that preferably not more than one of R_b and R_c is acyl, and with the proviso that if R_c is one of the mentioned moieties other than acyl then R_b can also be unsubstituted or substituted monocyclic aryl-alkyl; or R_b and R_c may form together a 3 to 7 membered nitrogen containing ring which can be unsubstituted or substituted;

Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;

R_e is hydrogen, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl; and

R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;

m is 0, 1 or 2;

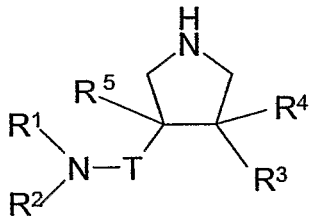
each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;

and T is methylene, methylene mono-substituted by alkyl, or is carbonyl or thiocarbonyl;

or a pharmaceutically acceptable salt thereof,

for use in the treatment of a mammal.

5. A compound of the formula I,



(I)

wherein

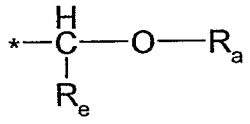
R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl;

with the proviso that if R^1 is one of the moieties mentioned in the definition of R^1 other than acyl then R^2 can also be unsubstituted or substituted monocyclic aryl-alkyl;

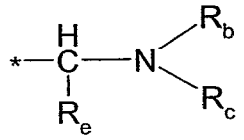
R^3 is a moiety selected from the group of moieties of the formulae

(a)

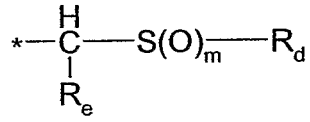


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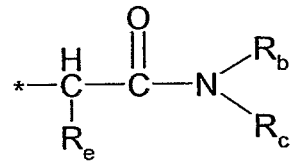
(b)



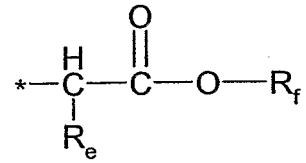
(c)



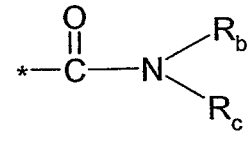
(d)



(e)

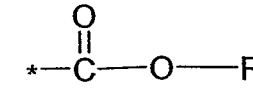


(f)



and

(g)



,

where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen, with the proviso that preferably not more than one of R_b and R_c is acyl, and with the proviso that if R_c is one of the mentioned moieties other than acyl then R_b can also be unsubstituted or substituted monocyclic aryl-alkyl; or R_b and R_c may form together a 3 to 7 membered nitrogen containing ring which can be unsubstituted or substituted;

Rd in a moiety of the formula (c) is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;

R_e is hydrogen, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl; and

R_f is substituted alkyl or preferably unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;

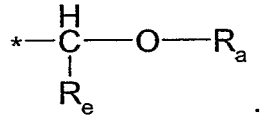
m is 0, 1 or 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;

and T is methylene, methylene mono-substituted by alkyl, carbonyl or thiocarbonyl;
or a salt thereof.

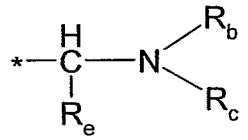
6. A compound of the formula I according to claim 5
wherein
R^1 is acyl;
R^2 is unsubstituted or substituted cycloalkyl or preferably unsubstituted or substituted alkyl,
R^3 is a moiety selected from the group of moieties of the formulae

(a)

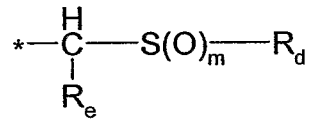


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(b)

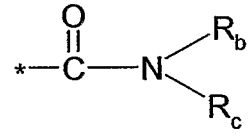


(c)



and

(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,
R_a is acyl or hydrogen;
R_b is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl or acyl;
R_c is hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl or preferably C_3-C_8-cycloalkyl, hydrogen or C_1-C_7-alkyl;
R_d is unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl;
R_e is hydrogen (preferred) or C_1-C_7-alkyl; and

m is 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;
and T is methylene, methylene mono-substituted by alkyl, carbonyl or thiocarbonyl;
or an (especially pharmaceutically acceptable) salt thereof.

7. The use according to any one of claims 1 to 3, the compound of the formula I or a pharmaceutically acceptable salt thereof for use according to claim 4 or the compound of formula I or a salt thereof according to any one of claims 5 or 6, wherein one or more, preferably all of the substituent and symbol definitions where mentioned are as follows:

"C_1-C_7-" defines a moiety with up to and including maximally 7, especially up to and including maximally 4, carbon atoms, said moiety being branched one or more times or straight-chained and bound via a terminal or a non-terminal carbon, for example, C_1-C_7-alkyl is n-pentyl, n-hexyl or n-heptyl or preferably C_1-C_4-alkyl, especially methyl, ethyl, n-propyl, sec-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl;

halo or halogen is fluoro, chloro, bromo or iodo, most preferably fluoro, chloro or bromo;

unsubstituted or substituted mono- or bicyclic aryl is a mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, and is unsubstituted or substituted by one or more, especially one to three, moieties, preferably independently selected from the group consisting of

a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H (especially in substituted aryl or substituted aryl-alkyl as R^1) where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or (with lower preference) substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkanoyl, naphthyl-C_1-C_7-alkanoyl, phenyl,

naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; e.g. the substituent of said formula is C_1-C_7-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, such as 3-methoxypropyl or 2-methoxyethyl, C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyloxy- or naphthyloxy-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, such as aminomethyl, C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl, mono- or di- (C_1-C_7-alkyl-, naphthyl-, phenyl, naphthyl-C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-O-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-SO_2-NH-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7alkoxy, C_1-C_7-alkanoyloxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyloxy, halo-C_1-C_7-alkylthio, such as trifluoromethylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, mono- or di-(C_1-C_7-alkyl-, naphthyl-C_1-C_7-alkyl-, phenyl-C_1-C_7-alkyl- and/or C_1-C_7-alkoxy-C_1-C_7-alkyl-)amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkanoylamino, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonylamino, carboxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkoxycarbonyl, amino-C_1-C_7-alkoxy-carbonyl, (N-) mono-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkoxycarbonyl, N- mono- or N,N-di-(C_1-C_7-alkyl, naphthyl-C_1-C_7.alkyl and/ or phenyl-C_1-C_7-alkyl)-aminocarbonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, amino-C_1-C_7-alkylsulfonyl, N-mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylsulfonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylsulfonyl, N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl or N-mono- or N,N-di-(C_1-C_7-alkyl)-aminosulfonyl;

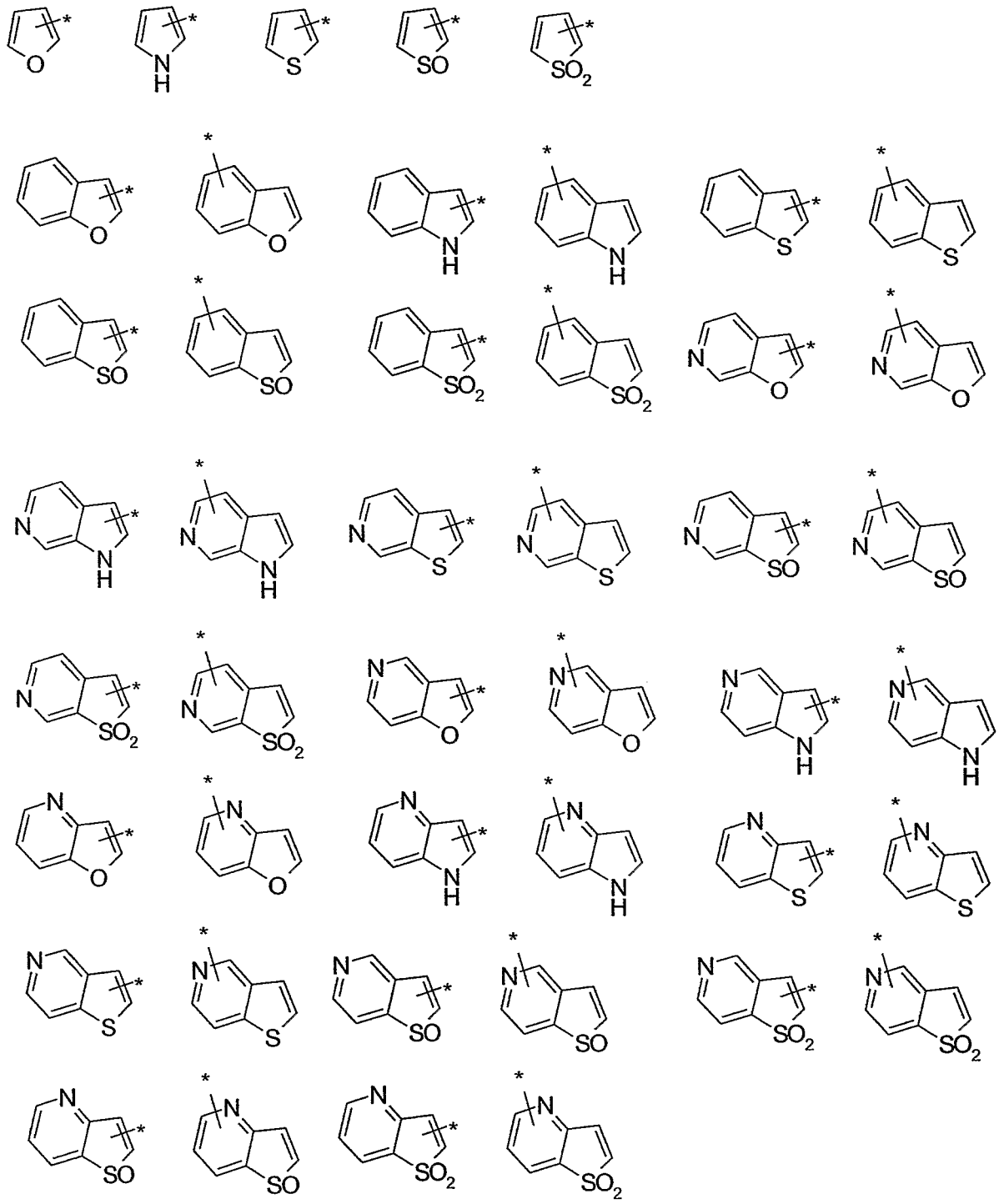
from C_2-C_7-alkenyl, C_2-C_7-alkynyl, phenyl, naphtyl, mono- or bicyclic heterocyclyl, especially as defined below for mono- or bicyclic heterocyclyl, preferably selected from pyrrolyl, furanyl, thienyl, pyrimidine-2,4-dione-1-, -3- or –5-yl and tetrahydrofuranyl, , phenyl- or naphthyl- or (mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl or C_1-C_7-alkyloxy wherein mono- or bicyclic heterocyclyl is as defined below, preferably selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl ; such as benzyl or naphthylmethyl, tetrahydrofuranyl- or

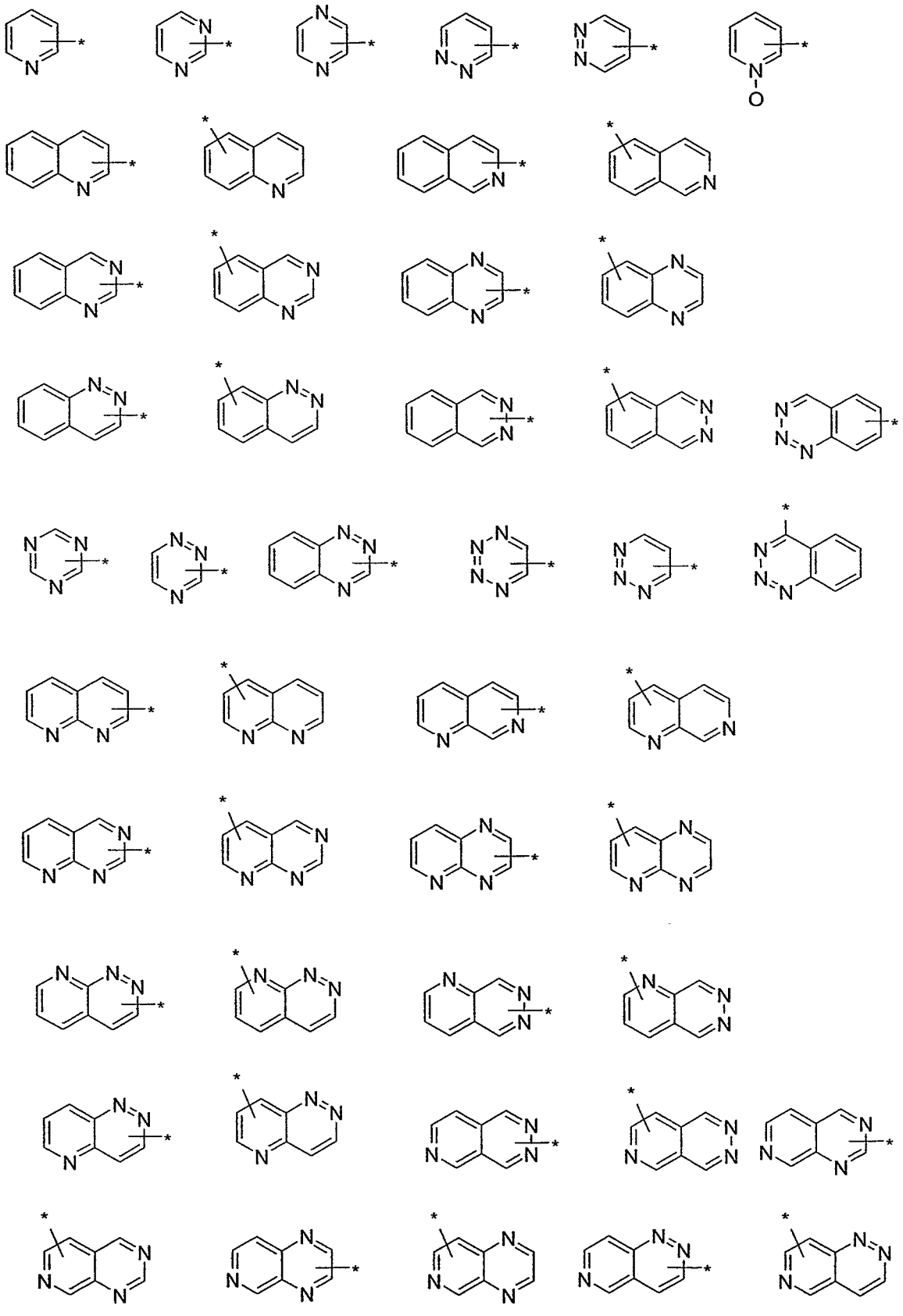
tetrahydropyranyl-C_1-C_7-alkyloxycarbonyl, benzoyl- or naphthoylamino-C_1-C_7-alkyl, (phenyl- or naphthyl- or mono- or bicyclic heterocyclyl)-sulfonylamino-C_1-C_7-alkyl (wherein phenyl or naphthyl or mono- or bicyclic heterocyclyl is unsubstituted or substituted, preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, halo, hydroxy, phenyl-C_1-C_7-alkoxy wherein phenyl is preferably unsubstituted or substituted, preferably by C_1-C_7-alkoxy and/or halo, mono- or bicyclic heterocyclyl-C_1-C_7-alkoxy, (mono- or bicyclic heterocyclyl or phenyl or naphthyl)-oxy, naphthyl-C_1-C_7-alkyloxy, benzoyl, naphthoyl or mono- or bicyclic heterocyclylcarbonyl)-oxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonyloxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-thio, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-thio, nitro, amino, di-((naphthyl or phenyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl)-amino, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-amino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxycarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyloxycarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, amino-C_1-C_7-alkylcarbonyl, (N-) mono- or (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylcarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxy-carbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkoxycarbonyl, (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono or N,N-di-(naphthyl or phenyl or mono- or bicyclic heterocyclyl)-aminocarbonyl, cyano, C_1-C_7-alkylene which is unsubstituted or substituted by up to four C_1-C_7-alkyl substituents and bound to two adjacent ring atoms of the aryl moiety, sulfenyl, sulfinyl, C_1-C_7-alkylsulfinyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfinyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl,

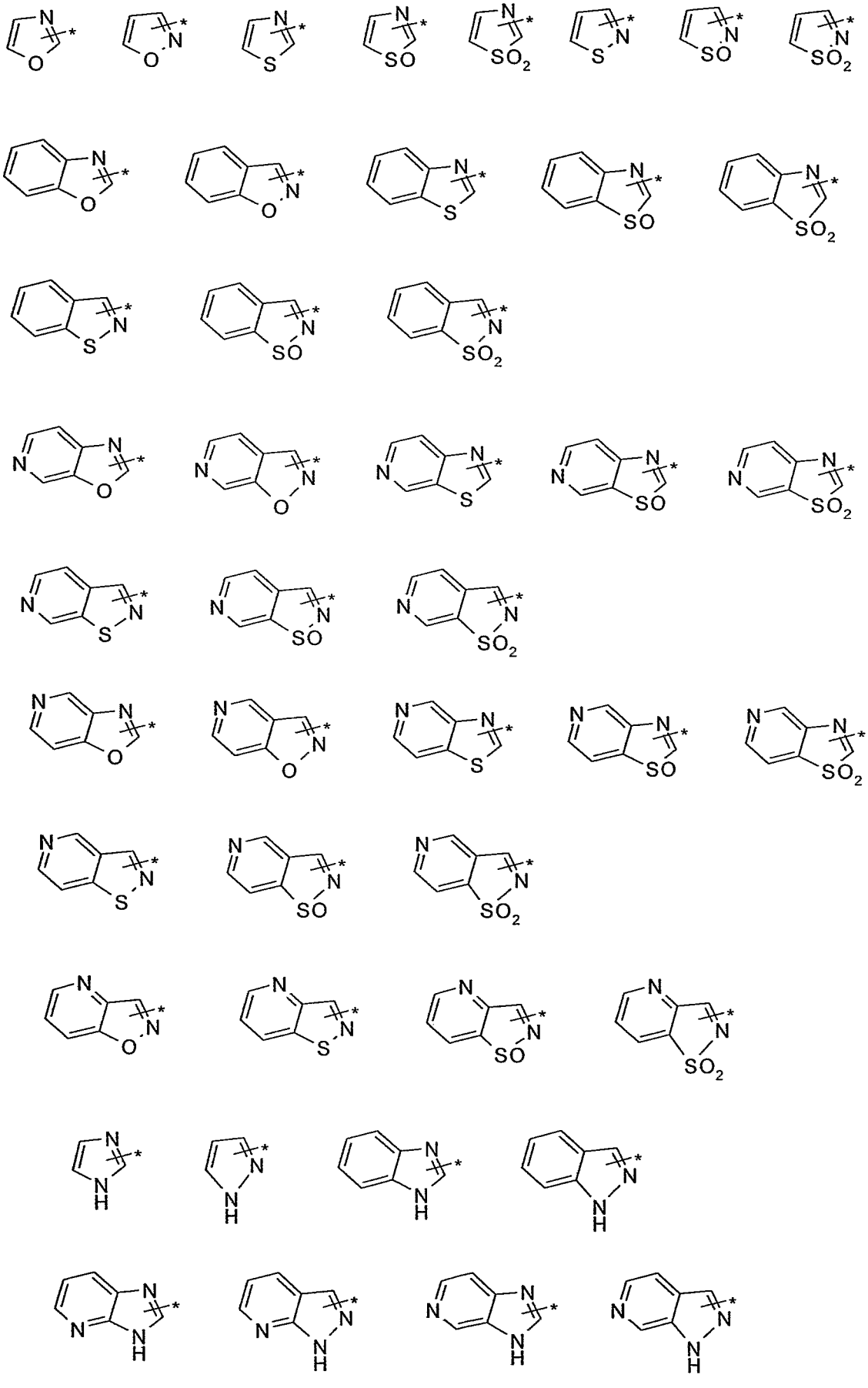
phenyl-, naphthyl, mono- or bicyclic heterocyclyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl-C_1-C_7-alkyl)-aminosulfonyl;

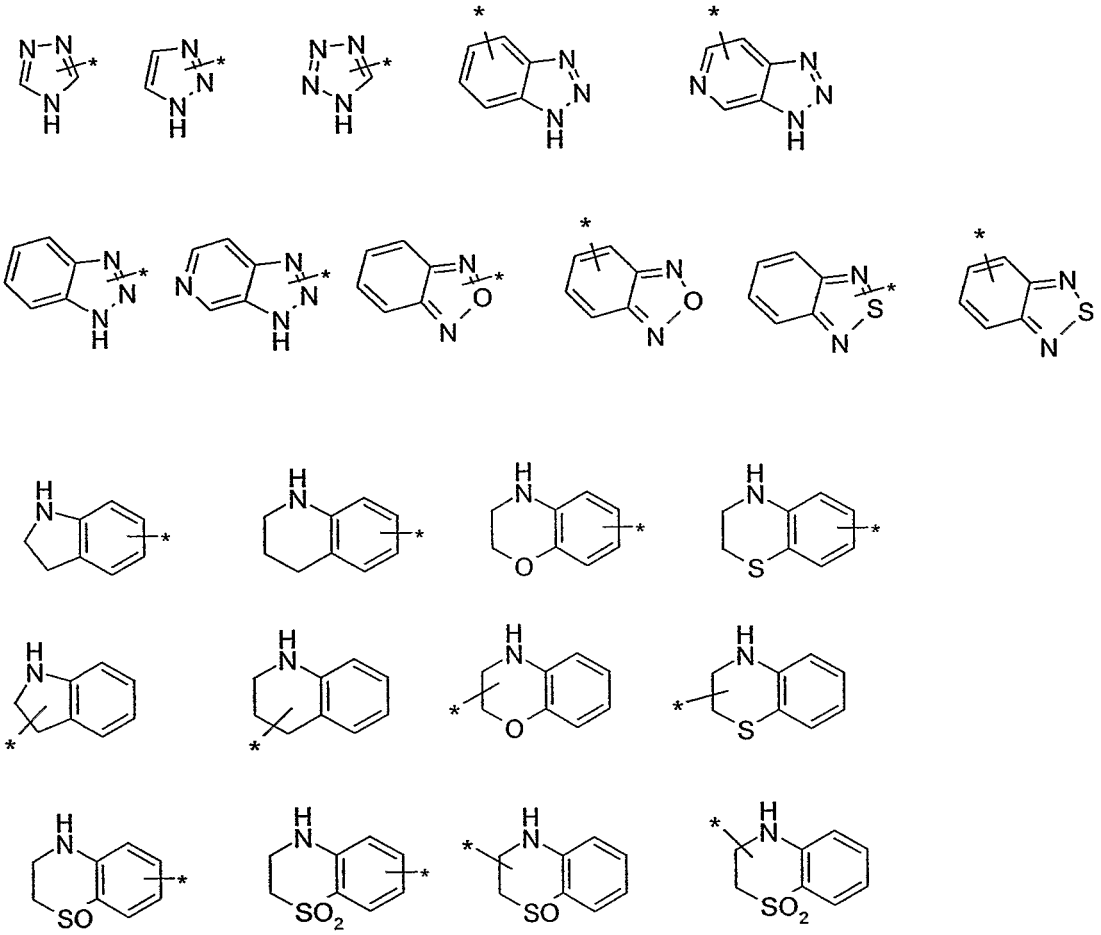
where any phenyl or naphthyl or mono- or bicyclic heterocyclyl (which mono- or bicyclic heterocyclyl is preferably as defined for mono- or bicyclic heterocyclyl, more preferably is selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl) mentioned as substituent of or as part of a substituent of substituted aryl is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, halo, especially fluoro, chloro, bromo or iodo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents;

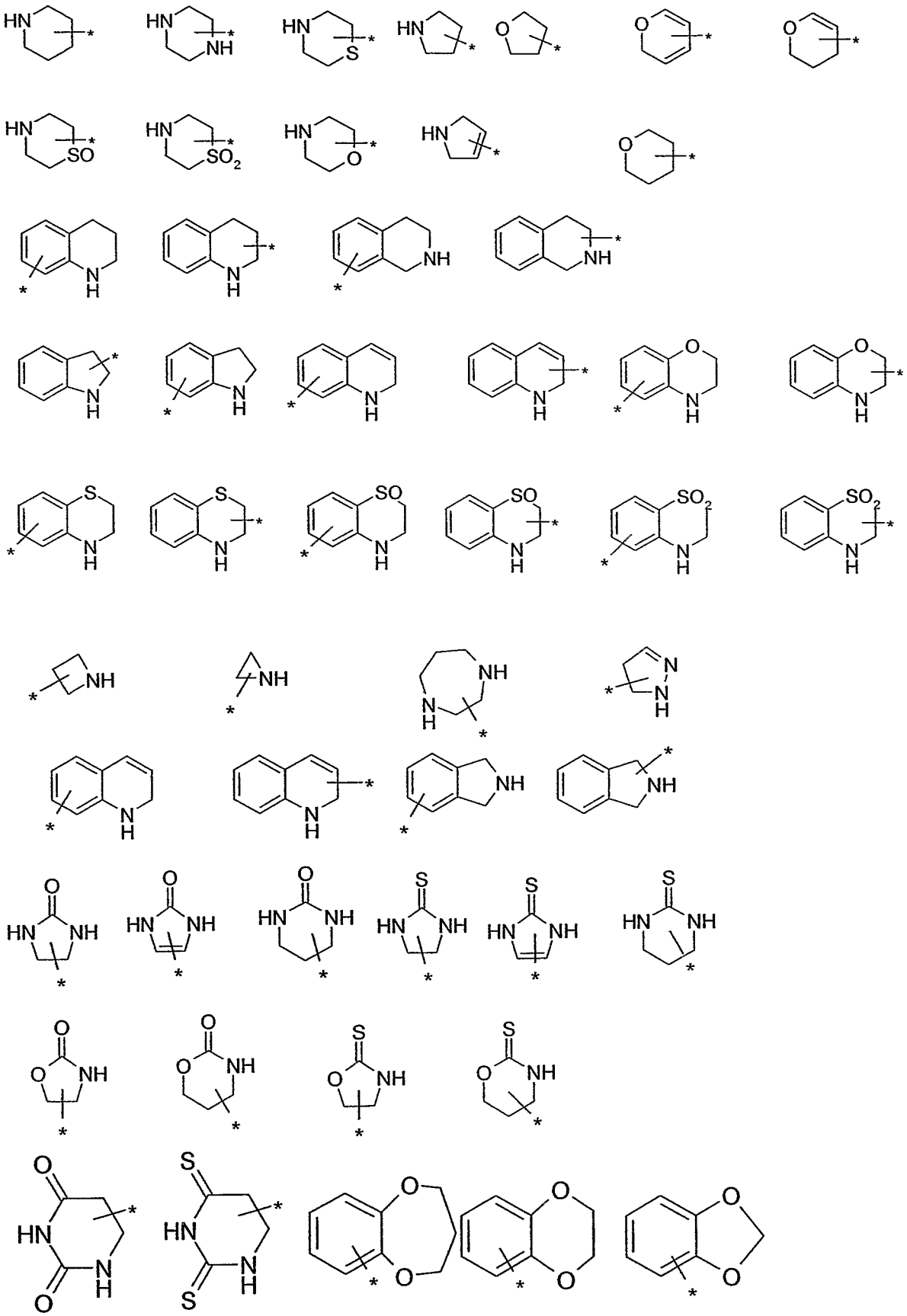
unsubstituted or substituted mono- or bicyclic heterocyclyl is a mono- or bicyclic heterocyclic moiety with an unsaturated, partially saturated or saturated ring system with preferably 3 to 22, more preferably 3 to 14, ring atoms and with one or more, preferably one to four, heteroatoms independently selected from nitrogen, oxygen and sulfur, which is unsubstituted or substituted by one or more, e.g. up to three, substitutents preferably independently selected from the substitutents mentioned above for aryl and from oxo (=O), imino (=NR) where R can be C_1-C_7-alkyl or hydrogen, and thioxo (=S), preferably oxo (=O) and thioxo (=S), where preferably, unsubstituted or substituted mono- or bicyclic heterocyclyl is selected from the following moieties:

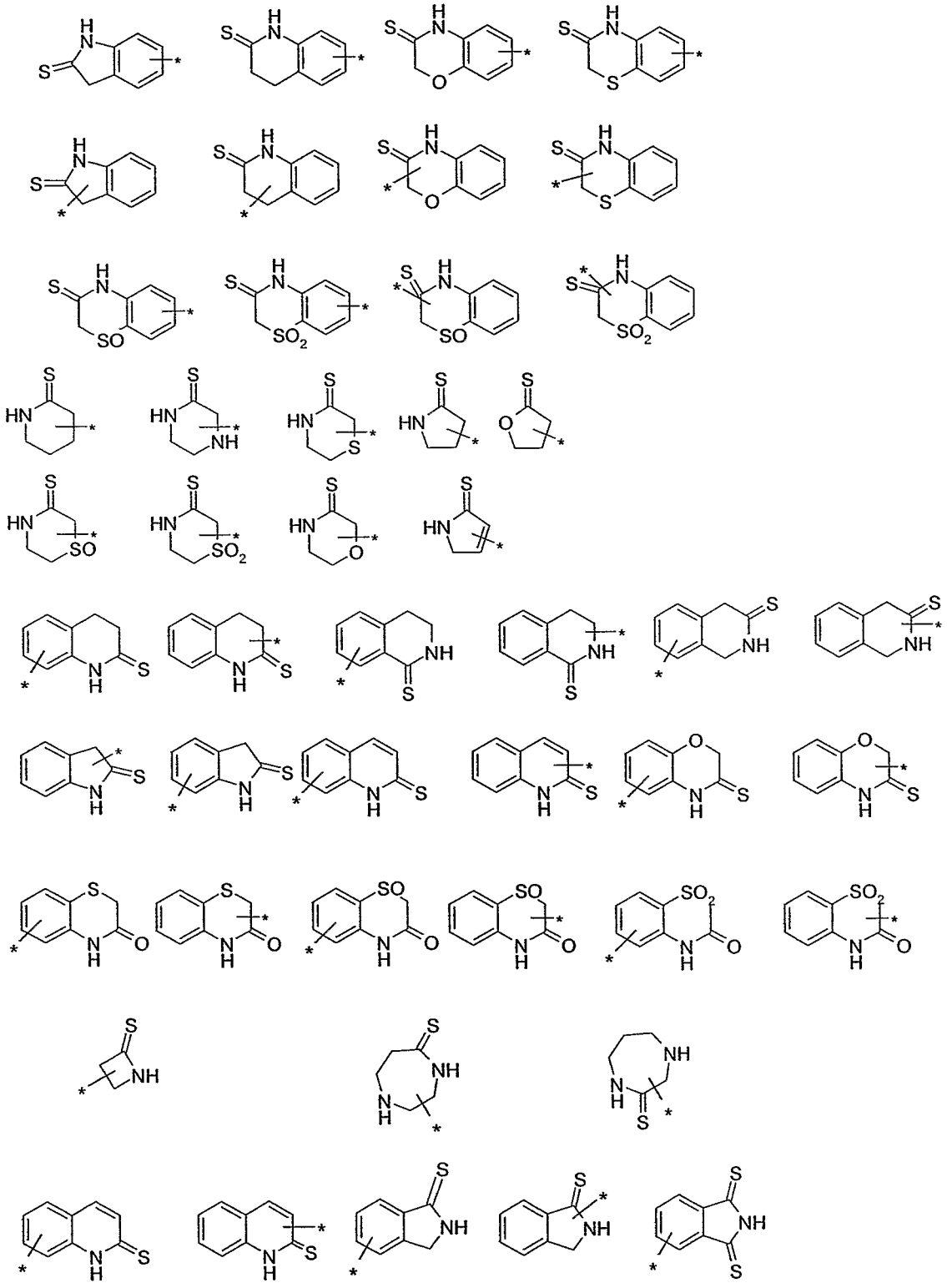


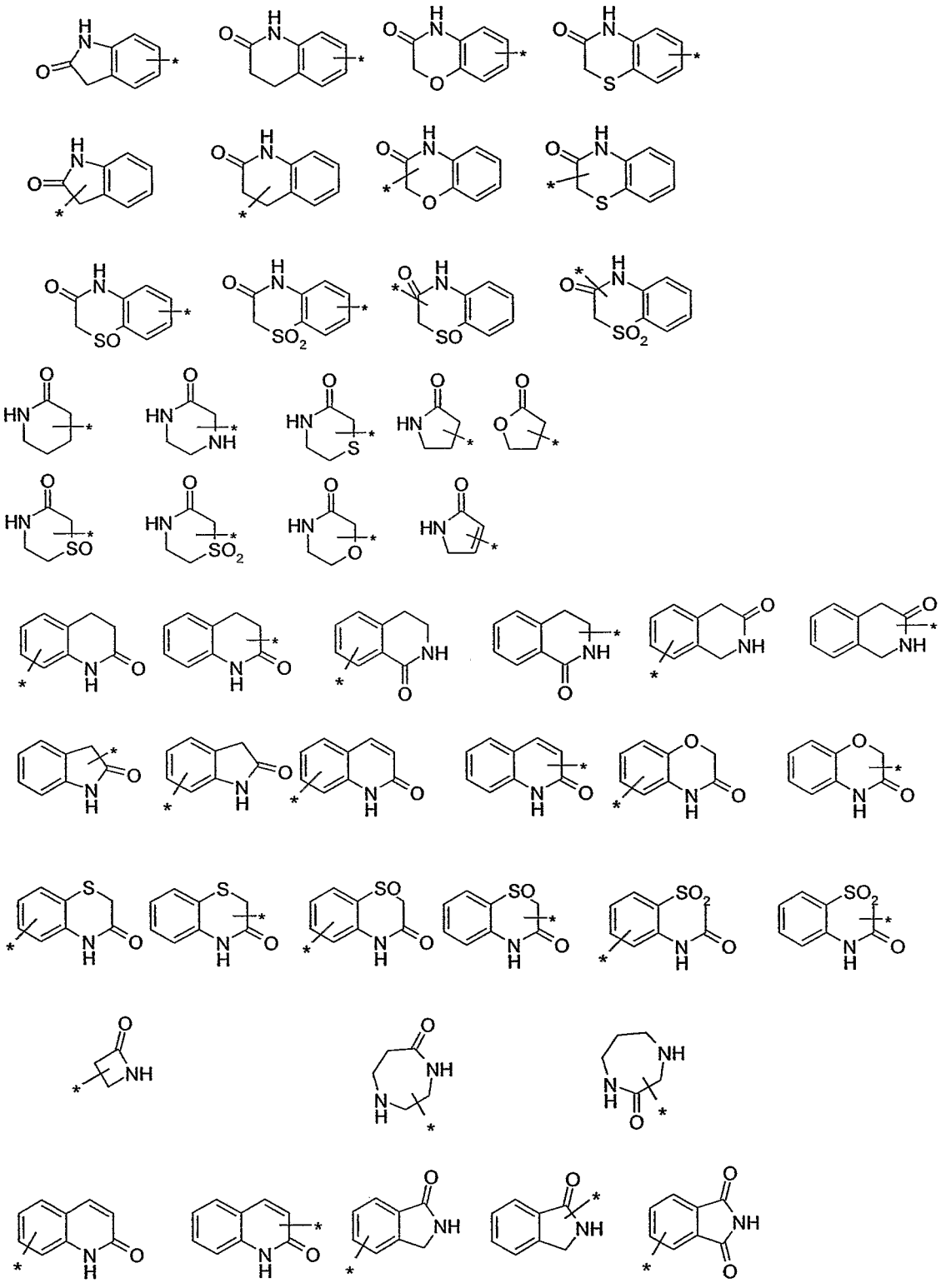












where in each case where an NH is present the bond with the asterisk connecting the respective heterocyclyl moiety to the rest of the molecule the H may be replaced with said

bond and/or the H may be replaced by a substituent (thus forming substituted imino), and one or more substituents may be present as just described;

unsubstituted or substituted mono- or bicyclic cycloalkyl is mono- or bicyclic, more preferably monocyclic, C_3-C_{16}, more preferably C_3-C_{10}-cycloalkyl, which may include one or more double (e.g. in cycloalkenyl) and/or triple bonds (e.g. in cycloalkinyl) with less double and/or triple bonds than required to form a fully unsaturated ring system; where preferably, mono- or bicyclic cycloalkyl is saturated; and where the mono- or bicyclic cycloalkyl is unsubstituted or substituted by one or more, e.g. one to three substitutents preferably independently selected from those mentioned above as substituents for aryl;

in unsubstituted or substituted mono- or bicyclic aryl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic aryl which is unsubstituted or substituted by one or more substituents, e.g. one to three substituents independently selected from those mentioned above as substituents for aryl and aryl is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above;

in unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic heterocyclyl is preferably as described above and is unsubstituted or substituted by one or more, e.g. up to three, substitutents independently selected from those mentioned above for substituted aryl, and from oxo (=O), imino (=NR) where R can be C_1-C_7-alkyl or hydrogen, and thioxo (=S), preferably oxo (=O) and thioxo (=S), and heterocyclyl is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above;

in unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic cycloalkyl is preferably as described above and is unsubstituted or substituted by one or more, e.g. up to three, substitutents independently selected from those mentioned above for substituted aryl, and cycloalkyl is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-

alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above;

acyl is preferably unsubstituted or substituted mono- or bicyclic aryl-carbonyl or -sulfonyl, unsubstituted or substituted mono- or bicyclic heterocyclylcarbonyl or -sulfonyl, unsubstituted or substituted mono- or bicyclic cycloalkylcarbonyl or -sulfonyl, formyl or (unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl or unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl)-carbonyl or -sulfonyl, or - especially if bound to N, S or O - unsubstituted or substituted alkyloxycarbonyl, unsubstituted or substituted mono- or bicyclic aryl-oxycarbonyl, unsubstituted or substituted mono- or bicyclic heterocyclyloxycarbonyl, unsubstituted or substituted mono- or bicyclic cyclo-alkyloxycarbonyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-oxycarbonyl , unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-oxycarbonyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-oxycarbonyl or N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl or -aminosulfonyl, with the proviso that–oxycarbonyl bound moieties are preferably bound to a nitrogen in the rest of the molecule; where preferred acyl moieties other than R^1 and/or R^2 where mentioned are C_1-C_7-alkanoyl, unsubstituted or (mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted)-phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkyl-carbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, unsubstituted or mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted) (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, C_1-C_7-alkylsulfonyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-

(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, or (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, napthyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl, mono- or bicyclic heterocyclyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl selected preferably from pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, 1H-indazanyl, benzofuranyl, benzothiophenyl, (more preferably) isoquinolinyl, quinolinyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, indolyl)-oxycarbonyl, and (tetrahydrofuranyl or tetrahydropyranyl)- C_1-C_7-alkyl oxycarbonyl, while as preferred acyl R^1 or R^2, indolyl-C_1-C_7-alkanoyl, -2,3-dihydro-benzo[1,4]dioxine-carbonyl, quinolyl-C_1-C_7-alkanoyl or phenyl-C_1-C_7-alkanoyl, wherein indolyl, 2,3-dihydro-benzo[1,4]dioxine, quinolyl and phenyl are unsubstituted or substituted by a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; and optionally one or more, e.g. up to two, further substituents selected from the other substituents mentioned above for substituted aryl; where unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl and unsubstituted or substituted mono- or bicyclic cycloalkyl are preferably as defined above whereever they are mentioned as part of acyl, while unsubstituted or substituted alkyl is preferably as defined below;

unsubstituted or substituted alkyl is C_1-C_{20}-alkyl, more preferably C_1-C_7-alkyl, that is straight-chained or branched (one or, where appropriate, more times), which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from unsubstituted or substituted mono- or bicyclic heterocyclyl as described below, especially pyrrolyl, furanyl, thienyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuran-

onyl, tetrahydro-pyranyl, 1H-indazanyl, benzofuranyl, benzothiophenyl, isoquinolinyl, quinolinyl or especially indolyl, each of which is unsubstituted or substituted as described above for unsubstituted or substituted heterocyclyl, e.g. by one to three substitutents independently selected from halo, hydroxy, C_1-C_7-alkyl, cyano and C_1-C_7-alkanoyl; from unsubstituted or substituted mono- or bicyclic cycloalkyl as described above, especially cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl each of which is unsubstituted or substituted as described below for unsubstituted or substituted cycloalkyl; or especially from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, C_1-C_7-alkanoyloxy, (C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonyloxy, benzoyl- or naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, benzoyl- or naphthoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylcarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl, sulfonyl, C_1-C_7-alkylsulfinyl, phenyl- or naphthylsulfinyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonylamino or –aminocarbonyloxy and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino;

where any phenyl or naphthyl mentioned as substituent of or as part of a substituent of substituted alkyl is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, halo, especially fluoro, chloro, bromo or iodo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl,

phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents;

unsubstituted or substituted alkenyl is preferably C_2-C_{20}-alkenyl, more preferably C_2-C_7-alkenyl with one or, if possible, more double bonds, that is straight-chained or branched one or, where appropriate, more times, which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from those mentioned as substituents for subsituted alkyl and from unsubsituted or substituted mono- or bicyclic aryl, each as described above;

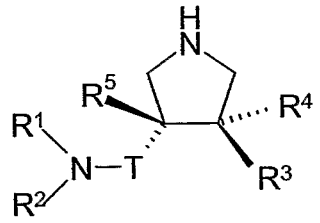
unsubstituted or substituted alkynyl is preferably C_2-C_{20}-alkynyl, more preferably C_2-C_7-alkynyl with one or, if possible, more triple bonds, that is straight-chained or branched one or, where appropriate, more times, which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from those mentioned as substituents for subsituted alkyl and from unsubsituted or substituted mono- or bicyclic aryl,;

esterified hydroxy is preferably acyloxy with acyl as defined above, more preferably C_1-C_7-alkanoyloxy or benzoyloxy;

etherified hydroxy is unsubstituted or preferably substituted C_1-C_7-alkyloxy wherein substituted alkyl is preferably as defined above, unsubstituted or substituted mono- or bicyclic aryloxy, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyloxy, unsubstituted or substituted mono- or bicyclic heterocyclyloxy, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyloxy, unsubstituted or substituted mono- or bicyclic cycloalkyloxy or unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyloxy, where in each case the moieties are preferably defined as above, or more preferably unsubstituted alkyloxy, especially C_1-C_7-alkyloxy; and

the 3 to 7 membered nitrogen containing ring formed by R_b and R_c which can be unsubstituted or substituted is a fully saturated, partially unsaturated or aromatic hydrocarbon ring, preferably a fully saturated hydrocarbon ring, and is preferably unsubstituted or substituted by one or more, e.g. one to four substitutents preferably independently selected from those mentioned above as substituents for aryl, especially a 4- to 7-membered ring that is unsubstituted or substituted by up to four substituents, such as one substituent, selected from hydroxy, halo, such as chloro, C_1-C_7-alkyl, such as methyl, cyano, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkanoyl, such as acetyl, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, hydroxy-C_1-C_7-alkoxy, and C_1-C_7-alkoxy-C_1-C_7-alkoxy; preferably a pyrrolidine or piperidine ring is formed by R_b and R_c that is substituted by up to four moieties selected from C_1-C_7-alkyl, hydroxyl, halo, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl and cyano, or is preferably unsubstituted.

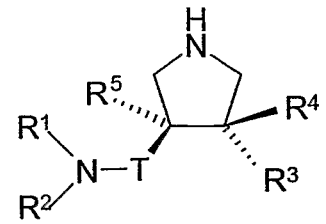
8. The use according to any one of claims 1 to 3 or 7, the compound of the formula I or a pharmaceutically acceptable salt thereof for use according to claim 4 or 7, or the compound of formula I or a salt thereof according to any one of claims 5 to 7, wherein formula I has the configuration given in formula IA



(IA);

wherein R^1, R^2, R^3, R^4, R^5 and T are as described in any one of the referenced claims.

9. The use according to any one of claims 1 to 3 or 7, the compound of the formula I or a pharmaceutically acceptable salt thereof for use according to claim 4 or 7, or the compound of formula I or a salt thereof according to any one of claims 5 to 7, wherein formula I has the configuration given in formula IB



(IB);

wherein R^1, R^2, R^3, R^4, R^5 and T are as described in any one of the referenced claims.

10. The use according to claim 1 of a compound of the formula I, wherein
R^1 is phenyl, naphthyl, mono- or bicyclic heterocyclyl, phenylcarbonyl, phenylacetyl, naphthylcarbonyl, naphthylacetyl, mono- or bicyclic heterocyclylcarbonyl or -acetyl, phenylsulfonyl, naphthylsulfonyl or mono- or bicyclic heterocyclylsulfonyl; wherein mono- or bicyclic heterocyclyl is pyrrolyl, furanyl, thienyl thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazolyl, benzofuranyl, benzothiophenyl or more preferably isoquinolyl, quinolyl or especially indolyl or -2,3-dihydro-benzo[1,4]dioxine, and each such mono- or bicyclic heterocyclyl, phenyl or naphthyl mentioned is unsubstituted or preferably substituted by one or more, especially one to three, moieties, preferably independently selected from the group consisting of
(i) a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkanoyl, naphthyl-C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; e.g. C_1-C_7-alkyl, halo-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyloxy- or naphthyloxy-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, such as aminomethyl, C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl, mono- or di- (C_1-C_7-alkyl-, naphthyl-, phenyl, naphthyl-C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-O-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-SO_2-NH-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, phenyl- or naphthyl-C_1-C_7-

alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyloxy, halo-C_1-C_7-alkylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, mono- or di-(C_1-C_7-alkyl-, naphthyl-C_1-C_7-alkyl-, phenyl-C_1-C_7-alkyl- and/or C_1-C_7-alkoxy-C_1-C_7-alkyl-)amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkanoylamino, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonylamino, carboxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkoxycarbonyl, amino-C_1-C_7-alkoxycarbonyl, (N-) mono-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkoxycarbonyl, N-mono- or N,N-di-(C_1-C_7-alkyl, naphthyl-C_1-C_7.alkyl and/ or phenyl-C_1-C_7-alkyl)-aminocarbonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, amino-C_1-C_7-alkylsulfonyl, N-mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylsulfonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylsulfonyl, N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl or N-mono- or N,N-di-(C_1-C_7-alkyl)-aminosulfonyl,

(ii) from C_2-C_7-alkenyl, C_2-C_7-alkynyl, phenyl, naphthyl, mono- or bicyclic heterocyclyl, especially as defined below for mono- or bicyclic heterocyclyl, preferably selected from pyrrolyl, furanyl, thienyl, pyrimidine-2,4-dione-1-, -3- or –5-yl, tetrahydropyranyl and tetrahydrofuranyl, phenyl- or naphthyl- or (mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl or C_1-C_7-alkyloxy wherein mono- or bicyclic heterocyclyl is as defined below, preferably selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl; tetrahydrofuranyl- or tetrahydropyranyl-C_1-C_7-alkyloxycarbonyl, benzoyl- or naphthoylamino-C_1-C_7-alkyl, (phenyl- or naphthyl- or mono- or bicyclic heterocyclyl)-sulfonylamino-C_1-C_7-alkyl, wherein phenyl or naphthyl or mono- or bicyclic heterocyclyl is unsubstituted or substituted, preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, halo, hydroxy, phenyl-C_1-C_7-alkoxy wherein phenyl is preferably unsubstituted or substituted, preferably by C_1-C_7-alkoxy and/or halo, mono- or bicyclic heterocyclyl-C_1-C_7-alkoxy, (mono- or bicyclic heterocyclyl or phenyl or naphthyl)-oxy, naphthyl-C_1-C_7-alkyloxy, benzoyl or naphthoyl or mono- or bicyclic heterocyclylcarbonyl)-oxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonyloxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-thio, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-thio, nitro, amino, di-((naphthyl or phenyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl)-amino, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-amino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-

aminocarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxycarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyloxycarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, amino-C_1-C_7-alkylcarbonyl, (N-) mono- or (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylcarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxy-carbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkoxycarbonyl, (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono or N,N-di-(naphthyl or phenyl or mono- or bicyclic heterocyclyl)-aminocarbonyl, cyano, C_1-C_7-alkylene which is unsubstituted or substituted by up to four C_1-C_7-alkyl substituents and bound to two adjacent ring atoms of the aryl moiety, sulfenyl, sulfinyl, C_1-C_7-alkylsulfinyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfinyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, mono- or bicyclic heterocyclyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl-C_1-C_7-alkyl)-aminosulfonyl;

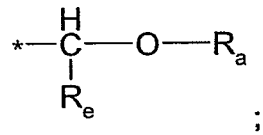
where any phenyl or naphthyl or mono- or bicyclic heterocyclyl - which mono- or bicyclic heterocyclyl is preferably as defined for mono- or bicyclic heterocyclyl, more preferably is selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl - mentioned as substituent of or as part of a substituent of mono- or bicyclic heterocyclyl, phenyl or naphthyl R^1 under (i) or (ii) is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, halo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-

alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents;

R^2 is phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl, wherein each phenyl or naphthyl mentioned so far in the definition of R^2 is unsubstituted or substituted as just described for substituted phenyl or naphthyl in the definition of R^1, or is preferably C_3-C_8-cycloalkyl or is C_1-C_7-alkyl that is unsubstituted or substituted by one or more, especially up to three, e.g. one or two, substituents independently selected from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, C_1-C_7-alkanoyloxy, (C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonyloxy, benzoyl- or naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, such as trifluoromethylthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, benzoyl- or naphthoylamino, phenyl- or naphthyl-C_1-C_7-alkylcarbonylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl, sulfonyl, C_1-C_7-alkylsulfinyl, phenyl- or naphthylsulfinyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonylamino or –aminocarbonyloxy and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino; or is C_3-C_{10}-cycloalkyl or C_3-C_{10}-cycloalkyl-C_1-C_7-alkyl;

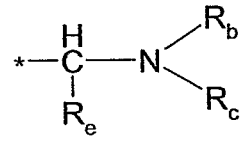
R^3 is a moiety selected from the group of moieties of the formulae

(a)

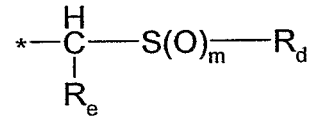


;

(b)

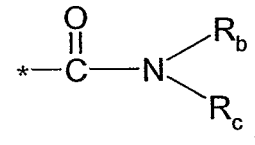


(c)



and

(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is acyl selected from C_1-C_7-alkanoyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted) phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkylcarbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]-aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl; or is hydrogen;

R_b is C_1-C_7-alkyl or – in each case unsubstituted or substituted - phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from the group consisting of C_1-C_7-alkyl, C_2-C_7-alkenyl, C_2-C_7-alkinyl, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl,

such as trifluoromethyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, C_1-C_7-alkoxy-carbonyl, carboxy-C_1-C_7-alkyl, halo, hydroxy, halo-C_1-C_7-alkoxy, halo-C_1-C_7-alkylthio, nitro, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, carbamoyl, cyano, C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl) -aminosulfonyl; or is acyl e.g. as just defined under R_a, in particular C_1-C_7-alkanoyl, unsubstituted or (mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted)-phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkyl-carbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, unsubstituted or mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted) (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, C_1-C_7-alkylsulfonyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, or (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, napthyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl, mono- or bicyclic heterocyclyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl selected preferably from pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, 1H-indazanyl, benzofuranyl, benzothiophenyl, (more preferably) isoquinolinyl, quinolinyl, tetrahydrofuran-onyl, tetrahydropyranyl, indolyl)-oxycarbonyl, and (tetrahydrofuranyl or tetrahydropyranyl)- C_1-C_7-alkyl oxycarbonyl, or selected from unsubstituted mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, C_1-C_7-alkylsulfonyl;

R_c is hydroxy-C_1-C_7-alkyl or C_1-C_7-alkyloxy-C_1-C_7-alkyl, C_3-C_8-cycloalkyl C_1-C7-alkyl or preferably C_3-C_8-cycloalkyl, hydrogen or C_1-C_7-alkyl;

R_d is unsubstituted or substituted phenyl- or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents in-

dependently selected from those mentioned for unsubstituted of substituted phenyl- or naphthyl-C_1-C_7-alkyl under R_b, or is -$N(R_b)(R_c)$;
R_e is C_1-C_7-alkyl or preferably hydrogen; and
m is 2;

each of R^4 and R^5 is selected, independently from the other, from C_1-C_7-alkyl, hydroxy, C_1-C_7-alkyloxy and preferably hydrogen;
and T is carbonyl or preferably methylene;

or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin, especially hypertension.

11. A compound of the formula I according to claim 5, wherein
R^1 is phenyl, naphthyl, mono- or bicyclic heterocyclyl, phenylcarbonyl, phenylacetyl, naphthylcarbonyl, naphthylacetyl, mono- or bicyclic heterocyclylcarbonyl or -acetyl, phenylsulfonyl, naphthylsulfonyl or mono- or bicyclic heterocyclylsulfonyl; wherein mono- or bicyclic heterocyclyl is pyrrolyl, furanyl, thienyl thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazolyl, benzofuranyl, benzothiophenyl or more preferably isoquinolyl, quinolyl or especially indolyl or -2,3-dihydro-benzo[1,4]dioxine, and each such mono- or bicyclic heterocyclyl, phenyl or naphthyl mentioned is unsubstituted or preferably substituted by one or more, especially one to three, moieties, preferably independently selected from the group consisting of
(i) a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H (especially in substituted aryl or substituted aryl-alkyl as R^1) where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkanoyl, naphthyl-C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and

independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; e.g. C_1-C_7-alkyl, halo-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyloxy- or naphthyloxy-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, such as aminomethyl, C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl, mono- or di- (C_1-C_7-alkyl-, naphthyl-, phenyl, naphthyl-C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-O-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-SO_2-NH-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyloxy, halo-C_1-C_7-alkylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, mono- or di-(C_1-C_7-alkyl-, naphthyl-C_1-C_7-alkyl-, phenyl-C_1-C_7-alkyl- and/or C_1-C_7-alkoxy-C_1-C_7-alkyl-)amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkanoylamino, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonylamino, carboxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkoxycarbonyl, amino-C_1-C_7-alkoxycarbonyl, (N-) mono-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkoxycarbonyl, N- mono- or N,N-di-(C_1-C_7-alkyl, naphthyl-C_1-C_7.alkyl and/ or phenyl-C_1-C_7-alkyl)-aminocarbonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, amino-C_1-C_7-alkylsulfonyl, N-mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylsulfonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylsulfonyl, N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl or N-mono- or N,N-di-(C_1-C_7-alkyl)-aminosulfonyl,

(ii) from C_2-C_7-alkenyl, C_2-C_7-alkynyl, phenyl, naphthyl, mono- or bicyclic heterocyclyl, especially as defined below for mono- or bicyclic heterocyclyl, preferably selected from pyrrolyl, furanyl, thienyl, pyrimidine-2,4-dione-1-, -3- or –5-yl, tetrahydropyranyl and tetrahydrofuranyl, phenyl- or naphthyl- or (mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl or C_1-C_7-alkyloxy wherein mono- or bicyclic heterocyclyl is as defined below, preferably selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl; tetrahydrofuranyl- or tetrahydropyranyl-C_1-C_7-alkyloxycarbonyl, benzoyl- or naphthoylamino-C_1-C_7-alkyl, (phenyl- or naphthyl- or mono- or bicyclic heterocyclyl)-sulfonylamino-C_1-C_7-alkyl, wherein phenyl or naphthyl or mono- or bicyclic heterocyclyl is unsubstituted or substituted, preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, halo, hydroxy, phenyl-C_1-C_7-

alkoxy wherein phenyl is preferably unsubstituted or substituted, preferably by C_1-C_7-alkoxy and/or halo, mono- or bicyclic heterocyclyl-C_1-C_7-alkoxy, (mono- or bicyclic heterocyclyl or phenyl or naphthyl)-oxy, naphthyl-C_1-C_7-alkyloxy, benzoyl or naphthoyl or mono- or bicyclic heterocyclylcarbonyl)-oxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonyloxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-thio, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-thio, nitro, amino, di-((naphthyl or phenyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl)-amino, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-amino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxycarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyloxycarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, amino-C_1-C_7-alkylcarbonyl, (N-) mono- or (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylcarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxy-carbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkoxycarbonyl, (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono or N,N-di-(naphthyl or phenyl or mono- or bicyclic heterocyclyl)-aminocarbonyl, cyano, C_1-C_7-alkylene which is unsubstituted or substituted by up to four C_1-C_7-alkyl substituents and bound to two adjacent ring atoms of the aryl moiety, sulfenyl, sulfinyl, C_1-C_7-alkylsulfinyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfinyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, mono- or bicyclic heterocyclyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl-C_1-C_7-alkyl)-aminosulfonyl;

where any phenyl or naphthyl or mono- or bicyclic heterocyclyl - which mono- or bicyclic heterocyclyl is preferably as defined for mono- or bicyclic heterocyclyl, more preferably is selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl - mentioned

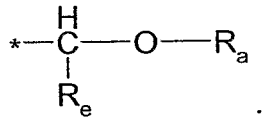
as substituent of or as part of a substituent of mono- or bicyclic heterocyclyl, phenyl or naphthyl R^1 under (i) or (ii) is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, halo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents;

R^2 is phenyl, naphthyl or naphthyl-C_1-C_7-alkyl, wherein each phenyl or naphthyl mentioned so far in the definition of R^2 is unsubstituted or substituted as just described for substituted phenyl or naphthyl in the definition of R^1; or is preferably C_3-C_8-cycloalkyl or is C_1-C_7-alkyl that is unsubstituted or substituted by one or more, especially up to three, e.g. one or two, substituents independently selected from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, C_1-C_7-alkanoyloxy, (C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonyloxy, benzoyl- or naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, such as trifluoromethylthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, benzoyl- or naphthoylamino, phenyl- or naphthyl-C_1-C_7-alkylcarbonylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl, sulfonyl, C_1-C_7-alkylsulfinyl, phenyl- or naphthylsulfinyl

wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonylamino or -aminocarbonyloxy and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino; or is C_3-C_{10}-cycloalkyl or C_3-C_{10}-cycloalkyl-C_1-C_7-alkyl;

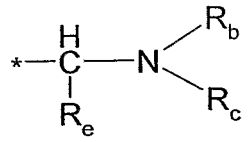
R^3 is a moiety selected from the group of moieties of the formulae

(a)

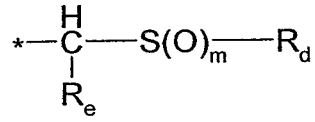


;

(b)

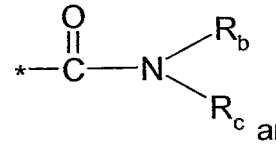


(c)



and

(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is acyl selected from C_1-C_7-alkanoyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted) phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkylcarbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-

C_1-C_7-alkyl-carbonyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]-aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl; or is hydrogen;

R_b is C_1-C_7-alkyl or – in each case unsubstituted or substituted - phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from the group consisting of C_1-C_7-alkyl, C_2-C_7-alkenyl, C_2-C_7-alkinyl, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, C_1-C_7-alkoxy-carbonyl, carboxy-C_1-C_7-alkyl, halo, hydroxy, halo-C_1-C_7-alkoxy, halo-C_1-C_7-alkylthio, nitro, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, carbamoyl, cyano, C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl) -aminosulfonyl; or is acyl as just defined under R_a or in particular

(a) unsubstituted or substituted mono- or bicyclic aryl-carbonyl, wherein the aryl moiety is preferably selected from phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, which is unsubstituted, mono- or di-substituted by C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, unsubstituted or substituted, preferably unsubstituted, heterocyclyl or unsubstituted or substituted, preferably unsubstituted, heterocyclyl-C_1-C_4-alkyl, such as heterocyclyl-CH_2, whereby the heterocyclyl moiety in each case is preferably monocyclic 5- or 6-membered heterocyclyl, preferably containing an N and/or O atom, such as tetrahydrofuranyl or tetrahydropyranyl, piperidinyl, pyrrolidinyl, piperazinyl or morpholinyl;

(b) unsubstituted or substituted mono- or bicyclic heterocyclylcarbonyl, wherein the heterocyclyl moiety is preferably selected from 5 to 11 membered ring systems which may be saturated, partially saturated or aromatic, and having preferably 1, 2 or 3 heteroatoms selected from O, N or S, including pyrrolidinyl, oxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, or tetrahydropyranyl; indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, benzofuranyl, 4H-benzo[1,4]oxazin-3-onyl, benzooxazolyl, benzo[1,2,5]oxadiazolyl, benzimidazolyl or 3,4-dihydro-2H-benzo[1,4]oxazinyl, whereby the heterocyclyl moiety is unsubstituted or is mono-substituted with -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably phenyl, -C_1-C_7-alkyl or C_3-C_8-cycloalkyl;

(c) unsubstituted or substituted mono- or bicyclic cycloalkylcarbonyl wherein the cycloalkyl moiety is preferably selected from C_3, C_4, C_5, C_6 and C_7-cycloalkyl which may be unsubstituted or mono-substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano;

(d) unsubstituted or substituted alkylcarbonyl wherein the alkyl moiety is preferably selected from branched or straight chain C_1-C_7-alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, methyl, ethyl or n-propyl, whereby the alkyl moiety is unsubstituted or preferably substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano;

(e) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkylcarbonyl, such as aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$C(CH_3)_2$-, wherein the alkyl moiety, in particular when aryl alkyl is aryl-CH_2- or aryl-CH_2CH_2-, may be mono-substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano or unsubstituted or substituted, preferably unsubstituted, phenyl, and wherein the aryl moiety is preferably selected from phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, which may be unsubstituted, mono-, di- or tri-substituted with C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably substituted, phenyl or naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano;

(f) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkylcarbonyl, such as heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2C(CH_3)_2$-, wherein the heterocyclyl moiety is preferably selected from 5 to 11 membered ring systems which may be saturated, partially saturated or aromatic, and having preferably 1, 2 or 3 heteroatoms selected from O, N or S, in particular pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, tetrahydrofuranyl, or tetrahydropyranyl; 4H-benzo[1,4]oxazin-3-onyl, benzooxazolyl, indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, benzofuranyl, benzo[1,2,5]oxadiazolyl, benzimidazolyl or 3,4-dihydro-2H-benzo[1,4]oxazinyl, whereby the heterocyclyl moiety is unsubstituted or is mono-substituted -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano;

(g) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkylcarbonyl, such as cycloalkyl-CH_2-, cycloalkyl-CH_2CH_2- or cycloalkyl-$CH_2C(CH_3)_2$-, whereby the alkyl moiety may be mono-substituted, including on the carbon where the cycloalkyl moiety is attached, with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and

cyano, and wherein the cycloalkyl moiety is preferably selected from C_3, C_5 and C_6-cycloalkyl, which may be unsubstituted or substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano;

(h) unsubstituted or substituted alkyloxycarbonyl, wherein the alkyl moiety is preferably selected from branched or straight chain C_1-C_7-alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, methyl, ethyl, n-propyl, n-butyl or n-pentyl, and which may be unsubsttituted or mono-substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano;

(i) unsubstituted or substituted mono- or bicyclic aryl-oxycarbonyl, wherein the aryl moiety is preferably selected from phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, which may be unsubstituted, mono- or di-substituted with C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, unsubstituted or substituted, preferably unsubstituted, heterocyclyl or unsubstituted or substituted, preferably unsubstituted, heterocyclyl-C_1-C_4-alkyl, such as heterocyclyl-CH_2, whereby the heterocyclyl moiety in each case is preferably monocyclic 5- or 6-membered heterocyclyl, preferably containing an N and/or O atom, such as tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl, pyrrolidin-2-onyl, piperazinyl or morpholinyl,

(j) unsubstituted or substituted mono- or bicyclic heterocyclyloxycarbonyl, wherein the heterocyclyl moiety is preferably selected from 5 to 7 membered ring systems which may be saturated, partially saturated or aromatic, and having 1, 2 or 3 heteroatoms selected from O, N or S, in particular pyrrolidinyl, oxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, or tetrahydropyranyl, wherein the heterocyclyl moiety is unsubstituted or mono-substituted with -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted,

preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano;

(k) unsubstituted or substituted mono- or bicyclic cycloalkyloxycarbonyl wherein the cycloalkyl moiety is preferably selected from C_3, C_4, C_5, C_6 and C_7-cycloalkyl which may be unsubstituted or substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano;

(l) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyloxycarbonyl, such as aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$CH(CH_2CH_3)$-, wherein the aryl moiety is preferably selected from phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, which may be unsubstituted or mono-substituted with C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably substituted, phenyl or naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano;

(m) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyloxycarbonyl, such as heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2CH(CH_3)$-, wherein the cycloalkyl moiety is preferably selected from 5 to 7 membered ring systems which may be saturated, partially saturated or aromatic, and having 1, 2 or 3, heteroatoms selected from O, N or S, such as pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, 1,3-dioxane, tetrahydrofuranyl, or tetrahydropyranyl; whereby the heterocyclyl moiety may be unsubstituted or substituted with -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, such as COMe, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano;

(n) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-oxycarbonyl, such as cycloalkyl-CH_2-, cycloalkyl-CH_2CH_2- or cycloalkyl-$CH_2CH(CH_3)$-, most preferably cycloalkyl-

CH_2-, wherein the cycloalkyl moiety is preferably selected from C_3 and C_5 –cycloalkyl, and may be unsubstituted or substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano,

(o) N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl, whereby

- the alkyl moiety of the unsubstituted or substituted alkyl aminocarbonyl is preferably branched or straight chain C_1-C_7-alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, methyl, ethyl, n-propyl, n-butyl or n-pentyl, which is unsubstituted or substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano;
- the aryl moiety of the unsubstituted or substituted aryl aminocarbonyl is preferably phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, which is unsubstituted or mono-substituted with C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano,
- the cycloalkyl moiety moiety of the unsubstituted or substituted cycloalkyl aminocarbonyl is preferably C_3 or C_6-cycloalkyl which may be unsubstituted or substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano;

- the aryl alkyl moiety of the unsubstituted or substituted aryl alkyl aminocarbonyl is preferably aryl-CH_2-, aryl-CH_2CH_2-, or aryl-$CH(CH_2CH_3)$-, whereby the alkyl moiety, in particular when aryl alkyl is aryl-CH_2-, may be mono-substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano or unsubstituted or substituted, preferably unsubstituted, phenyl, and whereby the aryl moiety is preferably phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl which is unsubstituted, mono-, di- or tri-substituted with C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano;

- the heterocyclyl alkyl moiety of the unsubstituted or substituted heterocyclyl alkyl aminocarbonyl is preferably heterocyclyl-CH_2- or heterocyclyl-CH_2CH_2-, whereby the heterocyclyl moiety is preferably are selected from 5 to 7 membered ring systems which may be aromatic or saturated rings, and having 1, 2 or 3, heteroatoms selected from O, N or S, such as pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, 1,3-dioxane, tetrahydrofuranyl, or tetrahydropyranyl; which may be unsubstituted or mono-substituted with -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, such as COMe, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano;

- the cycloalkyl alkyl moiety of the unsubstituted or substituted cycloalkyl alkyl aminocarbonyl is preferably cycloalkyl-CH_2-, whereby the cycloalkyl moiety is preferably selected from C_6 – cycloalkyl which may by unsubstituted or mono-substituted O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano;

When R_b is acyl, R_c is as defined herein, preferably, R_c is hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl, unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, or preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or unsubstituted or substituted C_1-C_7-alkyl, most preferably cyclopropyl or methyl. In particular, when R_b is acyl as defined under (h) to (n), R_c is preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or

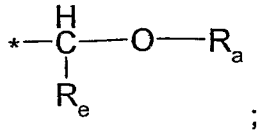
unsubstituted or substituted C_3-C_8-cycloalkyl C_1-C_7-alkyl or unsubstituted or substituted C_1-C_7-alkyl, most preferably cyclopropyl or methyl or ethyl, in particular, when R_b is acyl as defined under (o), R_c is preferably unsubstituted or substituted C_3-C_8-cycloalkyl most preferably cyclopropyl.
or R_b is selected from unsubstituted mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, C_1-C_7-alkylsulfonyl;
R_c is, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl, unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, or preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or unsubstituted or substituted C_1-C_7-alkyl;
R_d is unsubstituted or substituted phenyl- or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from those mentioned for unsubstituted of substituted phenyl- or naphthyl-C_1-C_7-alkyl under R_b , or is -$N(R_b)(R_c)$;
R_e is C_1-C_7-alkyl or preferably hydrogen; and
m is 2;

each of R^4 and R^5 is selected, independently from the other, from C_1-C_7-alkyl, hydroxy, C_1-C_7-alkyloxy and preferably hydrogen;
and T is carbonyl or preferably methylene;

or a salt thereof.

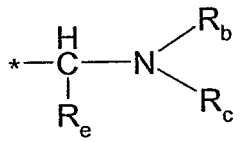
12. A compound of the formula I according to claim 5, wherein
R^1 is phenyl-, indolyl-, quinolyl- or 2,3-dihydro-benzo[1,4]dioxinyl-C_1-C_7-alkanoyl (preferably –carbonyl or –acetyl) wherein the phenyl, indolyl, quinolyl or 2,3-dihydro-benzo[1,4]dioxinyl is substituted by halo, C_1-C_7-alkyloxy-C_1-C_7-alkyloxy, C_1-C_7-alkylene-O-C_1-C_7-alkyl or C_1-C_7-alkyloxy-C_1-C_7-alkyloxy-C_1-C_7-alkyl and may further be substituted by one or more C_1-C_7-alkyl (especially methyl) and/or C_1-C_7-alkyloxy moieties;
R^2 is C_3-C_8-cycloalkyl or preferably C_1-C_7-alkyl ;
R^3 is a moiety selected from the group of moieties of the formulae

(a)

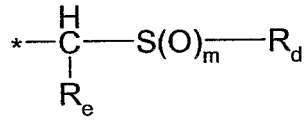


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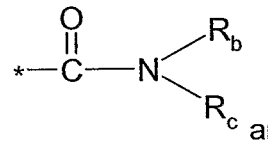
(b)



(c)



(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

wherein

R_a is hydrogen or N-mono- or N,N-di-(C_1-C_7-alkyl, (unsubstituted or halo-substituted) phenyl or naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl C_3-C_8-cycloalkyl-C_1-C_7-alkyl, heterocyclyl-C_1-C_7-alkyl, heterocyclyl and/or C_3-C_8-cycloalkyl)-aminocarbonyl;

each of R_b and R_c is, independently of the other, is selected from hydrogen, C_1-C_7-alkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, unsubstituted or substituted aryl such as phenyl, naphthyl, naphthyl-C_1-C_7-alkyl, or acyl such as C_3-C_8-cycloalkylcarbonyl, C_3-C_8cycloalkyl-C_1-C_7-alkylcarbonyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted phenyl- or naphthyl-C_1-C_7-alkanoyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, C_1-C_7-alkylsulfonyl or (unsubstituted or [C_1-C_7-alkyl-, halo-lower alkyl-, halo, C_1-C_7-alkyloxy-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted) (phenyl- or naphthyl)-C_1-C_7-alkylsulfonyl,

in particular acyl is selected from

(a) unsubstituted or substituted mono- or bicyclic aryl-carbonyl, wherein the aryl moiety is preferably selected from phenyl, indanyl, or 1,2,3,4-tetrahydronaphthyl which is unsubstituted, mono- or di-substituted by heterocyclyl, heterocyclyl-CH_2, -O-C_1-C_7-alkyl, -O-C_1-C_7-alkylene-O-alkyl and/or halo, whereby the heterocyclyl moiety in each case is preferably monocyclic 5- or 6-membered heterocyclyl, preferably containing an N and/or O

atom, such as tetrahydrofuranyl or tetrahydropyranyl, piperidinyl, pyrrolidinyl, piperazinyl or morpholinyl;

(b) unsubstituted or substituted mono- or bicyclic heterocyclylcarbonyl, wherein the heterocyclyl moiety is preferably selected from 5 to 11 membered ring systems which may be saturated, partially saturated or aromatic, and having preferably 1 or 2 heteroatoms selected from O and/or N, including pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, tetrahydropyranyl, indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, or 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, whereby the heterocyclyl moiety is unsubstituted or is mono-substituted with phenyl, -C_1-C_7-alkyl or C_3-C_8-cycloalkyl;

(c) unsubstituted or substituted mono- or bicyclic cycloalkylcarbonyl wherein the cycloalkyl moiety is preferably selected from C_3, C_4, C_5, C_6 and C_7-cycloalkyl which may be unsubstituted or mono-substituted with O-C_1-C_4-alkyl or hydroxy;

(d) unsubstituted or substituted alkylcarbonyl wherein the alkyl moiety is preferably selected from branched or straight chain C_1-C_7-alkyl such as isobutyl, isopentyl and 2,2-dimethyl-propyl, methyl, ethyl or n-propyl, whereby the alkyl moiety is mono-substituted with -O-C_1-C_7-alkyl, hydroxyl, C_1-C_7-alkanoylamino, unsubstituted or di-substituted phenyloxy, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl and C_1-C_7-alkyloxycarbonyl;

(e) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkylcarbonyl, such as aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$C(CH_3)_2$-, wherein the alkyl moiety, in particular when aryl alkyl is aryl-CH_2- or aryl-CH_2CH_2-, may be mono-substituted with unsubstituted phenyl, C_1-C_7-alkanoylamino, O-C_1-C_4-alkyl or hydroxyl, and wherein the aryl moiety is preferably selected from phenyl or naphthyl, which may be unsubstituted or substituted by -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, substituted phenyl, C_1-C_7-alkanoylamino and/or halo;

(f) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkylcarbonyl, such as heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2C(CH_3)_2$-, wherein the heterocyclyl moiety is preferably selected from 5 to 11 membered ring systems which may be saturated, partially saturated or aromatic, and having preferably 1or 2 heteroatoms selected from O and/or N, in particular pyrrolidinyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl, 4H-benzo[1,4]oxazin-3-onyl or benzooxazolyl, whereby the heterocyclyl moiety is unsubstituted or is mono-substituted with unsubstituted phenyl, -C_1-C_7-alkyl or C_1-C_7-alkanoyl;

(g) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkylcarbonyl, such as cycloalkyl-CH_2-, whereby the alkyl moiety may be mono-substituted, including on the carbon where the cycloalkyl moiety is attached, with -C_1-C_4-alkyl or hydroxyl, and wherein the cycloalkyl moiety is preferably selected from C_3, C_5 and C_6-cycloalkyl, which may be unsubstituted or mono-substituted with amino, O-C_1-C_4-alkyl or hydroxy;

(h) unsubstituted or substituted alkyloxycarbonyl, wherein the alkyl moiety is preferably selected from branched or straight chain C_1-C_7-alkyl such as isobutyl, isopentyl and 2,2-dimethyl-propyl, methyl or ethyl, and which may be mono-substituted with by -O-C_1-C_7-alkyl, C_1-C_7-alkanoylamino and N-mono- or N,N-di-substituted aminocarbonyl;

(i) unsubstituted or substituted mono- or bicyclic aryl-oxycarbonyl, wherein the aryl moiety is preferably selected from phenyl or naphthyl, which may be unsubstituted, mono-substituted with heterocyclyl or -O-C_1-C_7-alkyl, whereby the heterocyclyl moiety is monocyclic 5- or 6-membered heterocyclyl, containing an N and/or O atom, such as tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl, pyrrolidin-2-onyl, piperazinyl or morpholinyl;

(j) unsubstituted or substituted mono- or bicyclic heterocyclyloxycarbonyl, wherein the heterocyclyl moiety is preferably selected from 5 to 7 membered ring systems which may be saturated, partially saturated or aromatic, and having 1 or 2 heteroatoms selected from O and/or N, in particular tetrahydrofuranyl or tetrahydropyranyl, wherein the heterocyclyl moiety is unsubstituted;

(k) unsubstituted or substituted mono- or bicyclic cycloalkyloxycarbonyl wherein the cycloalkyl moiety is preferably selected from C_6-cycloalkyl which is unsubstituted;

(l) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyloxycarbonyl, such as aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$CH(CH_2CH_3)$-, wherein the aryl moiety is preferably selected from phenyl which is unsubstituted;

(m) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyloxycarbonyl, such as heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2CH(CH_3)$-, wherein the cycloalkyl moiety is preferably selected from 5 to 7 membered ring systems which may be saturated, partially saturated or aromatic, and having 1 or 2 heteroatoms selected from O and/or N, such as pyridyl, piperidyl, isoxazolyl, tetrahydrofuranyl, tetrahydropyranyl or 1,3-dioxane, which is unsubstituted or is mono-substituted with -C_1-C_7-alkyl or C_1-C_7-alkanoyl;

(n) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-oxycarbonyl, such as cycloalkyl-CH_2-, wherein the cycloalkyl moiety is preferably selected from C_3 and C_5-cycloalkyl, and may be unsubstituted or substituted with C_1-C_7-alkanoylamino,

(o) N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl, whereby

- the alkyl moiety of the unsubstituted or substituted alkyl aminocarbonyl is preferably branched or straight chain C_1-C_7-alkyl such as isopropyl, isobutyl, methyl or ethyl, which is unsubstituted;
- the aryl moiety of the unsubstituted or substituted aryl aminocarbonyl is preferably phenyl or naphthyl, which is unsubstituted,
- the cycloalkyl moiety moiety of the unsubstituted or substituted cycloalkyl aminocarbonyl is preferably C_3 or C_6-cycloalkyl which is unsubstituted;
- the aryl alkyl moiety of the unsubstituted or substituted aryl alkyl aminocarbonyl is preferably aryl-CH_2-, aryl-CH_2CH_2-, or aryl-$CH(CH_2CH_3)$-, whereby the alkyl moiety, in particular when aryl alkyl is aryl-CH_2-, may be mono-substituted with unsubstituted phenyl, and whereby the aryl moiety is preferably phenyl, which is unsubstituted;
- the heterocyclyl alkyl moiety of the unsubstituted or substituted heterocyclyl alkyl aminocarbonyl is preferably heterocyclyl-CH_2- whereby the heterocyclyl moiety is preferably are selected from 5 to 7 membered ring systems which may be aromatic or saturated rings, and having 1 or 2 heteroatoms selected from Oand/or N, such as furanyl or tetrahydropyranyl; which is unsubstituted;
- the cycloalkyl alkyl moiety of the unsubstituted or substituted cycloalkyl alkyl aminocarbonyl is preferably cycloalkyl-CH_2-, whereby the cycloalkyl moiety is preferably selected from C_6–cycloalkyl which is unsubstituted;

with the proviso that if R_c is hydrogen, C_1-C_7-alkyl, phenyl, naphthyl or naphthyl-C_1-C_7-alkyl, then R_b can also be phenyl-C_1-C_7-alkyl;

R_d is unsubstituted or [C_1-C_7-alkyl-, phenyl-, halo-lower alkyl-, halo, oxo-C_1-C_7-alkyl-, C_1-C_7-alkyloxy-, phenyl-C_1-C_7-alkoxy-, halo-C_1-C_7-alkyloxy-, phenoxy-, C_1-C_7-alkanoylamino-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted (phenyl- or naphthyl)-C_1-C_7-alkyl;

R_e is hydrogen; and

m is 2;

each of R^4 and R^5 is hydrogen; and

T is carbonyl or preferably methylene;

or a salt thereof.

13. A compound of the formula I according to claim 5, selected from the group of compounds:
N-((3S*,4S*)-4-{[(3-Acetylamino-3-methyl-butyryl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[2-(2-oxo-pyrrolidin-1-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({[2-(1-Acetylamino-cyclopentyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S*,4S*)-4-{[Cyclopropyl-(3,3-dimethyl-butyryl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({[2-(1-Acetylamino-cyclohexyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S*,4S*)-4-{[Cyclopropyl-(3-methyl-3-pyrrol-1-yl-butyryl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[2-(1-isobutyrylamino-cyclopentyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S*,4S*)-4-{[Cyclopropyl-(4-methyl-pentanoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[2-(2-methyl-benzooxazol-5-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S*,4S*)-4-{[(3-Cyclohexyl-propionyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S,4S)-4-{[Cyclopropyl-(3-cyclopropyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S,4S)-4-{[(3-Cyclopentyl-propionyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S,4S)-4-{[Cyclopropyl-(3,3-diphenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({Cyclopropyl-[2-(2,6-dimethyl-phenoxy)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-3-phenyl-butyryl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(1-Acetyl-piperidin-4-yl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-3-Acetylamino-3-phenyl-propionyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((R)-3-Acetylamino-3-phenyl-propionyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-3-hydroxy-3-phenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-3-hydroxy-3-phenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(3-furan-2-yl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(2-furan-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-methoxy-2-cyclohexyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-hydroxy-4-methyl-pentanoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Cyclohexanecarbonyl-cyclopropyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

Cycloheptanecarboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[(2-Cyclopentyl-acetyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[(2-Cyclohexyl-acetyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Benzoyl-cyclopropyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(4-fluoro-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Chloro-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({[2-(3-Chloro-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(2-methoxy-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(3,5-difluoro-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(2,3,5-trifluoro-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(3-trifluoromethyl-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({[2-(3,5-Bis-trifluoromethyl-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropyl-(3-pyrrolidin-1-yl-benzoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(3'-fluoro-biphenyl-3-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropyl-(3-chloro-6-methoxy-1-yl-benzoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropyl-(4-morpholin-4-ylmethyl-benzoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

1H-Indole-2-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

1H-Indole-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S*,4S*)-4-{[Cyclopropyl-(2-naphthalen-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(2-phenoxy-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropyl-((S)-2-phenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropyl-((R)-2-phenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-hydroxy-2-phenyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-2-hydroxy-2-phenyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-2-methoxy-2-phenyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-methoxy-2-phenyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

Tetrahydro-furan-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

Tetrahydro-furan-2-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(S)-Tetrahydro-pyran-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(R)-Tetrahydro-pyran-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

Tetrahydro-pyran-4-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[Cyclopropyl-(4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(cis-4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(trans-4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-tetrahydro-furan-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-2-tetrahydro-furan-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-tetrahydro-pyran-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-2-tetrahydro-pyran-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

(R)-1,2,3,4-Tetrahydro-naphthalene-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
(S)-1,2,3,4-Tetrahydro-naphthalene-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
N-((3S*,4S*)-4-{[Cyclopropyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
Chroman-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
2H-Chromene-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
(R)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
(S)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
2-Oxo-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
4,5,6,7-Tetrahydro-benzo[d]isoxazole-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
3a,4,5,6,7,7a-Hexahydro-benzo[d]isoxazole-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
N-((3S,4S)-4-{[(2-Benzo[d]isoxazol-3-yl-acetyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
1,4,5,6-Tetrahydro-cyclopentapyrazole-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
Isoxazole-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
5-Methyl-isoxazole-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
5-Cyclopropyl-isoxazole-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide
5-Phenyl-isoxazole-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

5-Methyl-pyrazine-2-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

Indan-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

5-Oxo-1-phenyl-pyrrolidine-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-Cyclopropyl-N-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-succinamide

N-Cyclopropyl-N-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N'-methyl-succinamide

N-Cyclopropyl-N-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-succinamic acid methyl ester

N-((3S,4S)-4-{[Cyclopropyl-(2-piperidin-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(2-methyl-2-phenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-2-phenyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Methoxy-2-phenyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-4-methyl-pentanoyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Methoxy-2-cyclohexyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-3-methyl-butyryl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Cyclohexyl-2-hydroxy-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-3-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((R)-3-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[(2-Furan-2-yl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Methoxy-3-methyl-butyryl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Methoxy-4-methyl-pentanoyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Benzoyl-methyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[(2-Cyclohexyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-[(3S*,4S*)-4-({[2-(3-methoxy-phenyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-3-(3-methoxy-propoxy)-benzamide

Indan-2-carboxylic acid [(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(R)-1,2,3,4-Tetrahydro-naphthalene-2-carboxylic acid [(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(S)-1,2,3,4-Tetrahydro-naphthalene-2-carboxylic acid [(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

Tetrahydro-pyran-4-carboxylic acid [(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-[(3S,4S)-4-({[2-(1-Hydroxy-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-[(3S,4S)-4-({[2-(4-methoxy-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-[(3S,4S)-4-({[2-(4-methoxy-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-3-(3-methoxy-propoxy)-benzamide

3,4-Dihydro-2H-benzo[b][1,4]dioxepine-2-carboxylic acid [(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-Isopropyl-4-methoxy-N-((3S,4S)-4-{[(cis-4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-((3S,4S)-4-{[(trans-4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-[(3S,4S)-4-(phenylacetylamino-methyl)-pyrrolidin-3-ylmethyl]-benzamide

Indan-2-carboxylic acid [(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-{(3S,4S)-4-[((S)-2-Cyclohexyl-2-methoxy-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-{(3S,4S)-4-[((R)-2-methoxy-2-phenyl-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-{(3S,4S)-4-[((S)-2-methoxy-2-phenyl-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-3-(3-methoxy-propoxy)-benzamide

N-{(3S,4S)-4-[((R)-2-Cyclohexyl-2-methoxy-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S,4S)-4-[(Ethyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Ethyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Cyclobutyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclobutyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-N-{(3S*,4S*)-4-[(isopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-N-((3S*,4S*)-4-{[isopropyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Cyclopropanecarbonyl-isobutyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Cyclobutanecarbonyl-isobutyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Isobutyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Isobutyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Cyclopropylmethyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropylmethyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid isopropyl-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-amide

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid ((3S,4S)-4-{[(2-cyclohexyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-isopropyl-amide

N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[(2-Cyclohexyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

4-Ethyl-N-isopropyl-3-(3-methoxy-propoxy)-N-((3S,4S)-4-{[methyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-benzamide

Tetrahydro-pyran-4-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-((3S,4S)-4-{[Cyclopropyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

Tetrahydro-pyran-4-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[(3-Acetylamino-3-methyl-butyryl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

4-Ethyl-N-((3S,4S)-4-{[((S)-2-hydroxy-2-phenyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(1-Acetyl-piperidin-4-yl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(1-Acetyl-piperidin-4-yl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

4-Ethyl-N-((3S,4S)-4-{[((S)-2-hydroxy-4-methyl-pentanoyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

4-Ethyl-N-((3S,4S)-4-{[((S)-2-hydroxy-3-methyl-butyryl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

Indan-2-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

4-Ethyl-N-isopropyl-3-(3-methoxy-propoxy)-N-{(3S,4S)-4-[(2-methyl-2-phenyl-propionylamino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

4-Ethyl-N-isopropyl-N-{(3S,4S)-4-[((R)-2-methoxy-2-phenyl-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-3-(3-methoxy-propoxy)-benzamide

4-Ethyl-N-[(3S,4S)-4-({[2-(1-hydroxy-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

5-Methyl-pyrazine-2-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(S)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(R)-2-Oxo-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(S)-2-Oxo-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-Cyclopropyl-N-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N'-methyl-succinamide

5-Methyl-pyrazine-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

Isoxazole-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

(R)-Tetrahydro-furan-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(S)-Tetrahydro-furan-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(R)-Tetrahydro-pyran-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(S)-Tetrahydro-pyran-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[Cyclopropyl-(cis-4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(trans-4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

(S)-Tetrahydro-pyran-3-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(R)-Tetrahydro-pyran-3-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

Tetrahydro-pyran-4-carboxylic acid [(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-((3S,4S)-4-{[methyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-methoxy-2-phenyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

(S)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[(S)-2-Methoxy-2-phenyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

(S)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid [(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-((3S,4S)-4-{[(3-Acetylamino-3-methyl-butyryl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[(S)-2-Hydroxy-2-phenyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

Tetrahydro-pyran-4-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-[(3S,4S)-4-({methyl-[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-benzamide

N-[(3S,4S)-4-({Cyclopropyl-[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Cyclohexyl-2-methoxy-acetyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Cyclohexyl-2-methoxy-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-3-methyl-butyryl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-[(3S,4S)-4-({[2-(1-Acetyl-piperidin-4-yl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-4-methyl-pentanoyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[(cis-4-Hydroxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((R)-3-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-3-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-[(3S,4S)-4-({[2-(1-Acetyl-piperidin-4-yl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(cis-4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[(2-Furan-2-yl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-hydroxy-4-methyl-pentanoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

Indan-2-carboxylic acid [(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-{(3S,4S)-4-[(2-methyl-2-phenyl-propionylamino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-{(3S,4S)-4-[(2-tetrahydro-pyran-4-yl-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

(S)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid [(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-((3S,4S)-4-{[methyl-((R)-2-tetrahydro-pyran-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-benzamide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-((3S,4S)-4-{[methyl-((S)-2-tetrahydro-pyran-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-2-tetrahydro-furan-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-tetrahydro-furan-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-Isopropyl-N-((3S,4S)-4-{[(cis-4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-Isopropyl-N-((3S,4S)-4-{[(trans-4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-Isopropyl-N-((3S,4S)-4-{[(cis-4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-Isopropyl-N-((3S,4S)-4-{[(trans-4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-4-methyl-benzamide

1-(3-Methoxy-propyl)-1H-indole-6-carboxylic acid isopropyl-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-amide

N-Cyclopropyl-N-{(3S,4S)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-methoxy-3-(3-methoxy-propoxy)-benzamide

Cyclopropyl-[(3S,4S)-4-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid benzyl ester

Cyclopropyl-[(3S,4S)-4-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid isobutyl ester

Cyclopropyl-[(3S,4S)-4-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-yl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid benzyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid benzyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid isobutyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid pyridin-4-ylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 1-methyl-piperidin-4-ylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 2-methoxy-ethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-ylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 2,2-dimethyl-propyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 1-methyl-cyclopropylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 2-acetylamino-2-methyl-propyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid phenyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 2-methyl-2-methylcarbamoyl-propyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 1-acetylamino-cyclopentylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 1-acetyl-piperidin-4-ylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 5-methyl-isoxazol-3-ylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid naphthalen-1-yl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid cyclopropylmethyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid isobutyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 4-methoxy phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid cyclohexyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid naphthalen-2-yl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-yl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 5-methyl-[1,3]dioxan-5-ylmethyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 3-(2-oxo-pyrrolidin-1-yl)-phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 3-morpholin-4-yl-phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (R)-1-(tetrahydro-furan-2-yl)methyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (R)-1-phenyl-propyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (R)-1-phenyl-ethyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 2-methoxy phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 3-methoxy-3-methyl-butyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (R)-(tetrahydro-furan-3-yl) ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (S)-(tetrahydro-furan-3-yl) ester

[(3S,4S)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 3-methoxy-3-methyl-butyl ester

[(3S,4S)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid tetrahydro-pyran-4-yl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-yl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (S)-(tetrahydro-furan-3-yl) ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid tetrahydro-pyran-4-yl ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid (S)-(tetrahydro-furan-3-yl) ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 3-methoxy-3-methyl-butyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 3-methoxy-3-methyl-butyl ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 4-methoxy phenyl ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid (R)-1-(tetrahydro-furan-2-yl)methyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 4-methoxy phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (R)-1-(tetrahydro-furan-2-yl)methyl ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 5-methyl-[1,3]dioxan-5-ylmethyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 5-methyl-isoxazol-3-ylmethyl ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 5-methyl-isoxazol-3-ylmethyl ester

Cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid benzyl ester

Cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-yl ester

Cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 4-methoxy phenyl ester

[(3S,4S)-4-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid tetrahydro-pyran-4-yl ester

[(3S,4S)-4-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid (R)-1-(tetrahydro-furan-2-yl)methyl ester

[(3S,4S)-4-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid (S)-(tetrahydro-furan-3-yl) ester

[(3S,4S)-4-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 5-methyl-[1,3]dioxan-5-ylmethyl ester

[(3S,4S)-4-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 3-methoxy-3-methyl-butyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid benzyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid isobutyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-yl ester

Benzyl-methyl-carbamic acid (3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Diisobutyl-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Benzyl-cyclopropyl-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Isobutyl-methyl-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-4-ylmethyl)-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-4-yl)-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclohexylmethyl-methyl-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Benzyl-cyclopropyl-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-4-ylmethyl)-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-3-ylmethyl)-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-4-yl)-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-4-yl)-carbamic acid (3S,4S)-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

((R)-1-Phenyl-propyl)-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

N-[(3S*,4S*)-4-(1-Cyclopropyl-3-furan-2-ylmethyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-(1-Cyclopropyl-3-furan-2-ylmethyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-(4-Methoxy benzyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-(4-Chloro benzyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-(4-Fluoro benzyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Cyclohexylmethyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[1-Cyclopropyl-3-(tetrahydro-pyran-4-ylmethyl)-ureidomethyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1-Cyclopropyl-3-phenethyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1-Cyclopropyl-3,3-diphenyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1-Cyclopropyl-3,3-diisopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Benzyl-1-cyclopropyl-3-methyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Benzyl-1-cyclopropyl-3-ethyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-(3-Benzyl-1-cyclopropyl-3-ethyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Benzyl-1,3-dicyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1-Cyclopropyl-3-phenyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Benzhydryl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-(3-Benzyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1,3-Dicyclopropyl-3-phenyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Cyclohexyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1-Cyclopropyl-3-naphthalen-1-yl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-(1-Cyclopropyl-3-naphthalen-2-yl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S,4S)-4-[1-Cyclopropyl-3-((R)-1-phenyl-propyl)-ureidomethyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-(1-Cyclopropyl-3-isobutyl-3-methyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S,4S)-4-[1-Cyclopropyl-3-((S)-1-phenyl-propyl)-ureidomethyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

(R)-3-Phenyl-pyrrolidine-1-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

4-Ethyl-3-(3-hydroxy-propoxy)-N-isopropyl-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-3-(3-hydroxy-propoxy)-N-isopropyl-4-methoxy-benzamide

N-{(3S*,4S*)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(4-methoxy-butyl)-benzamide

N-{(3S*,4S*)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-difluoromethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

8-(3-Methoxy-propoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid {(3S*,4S*)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-isopropyl-amide

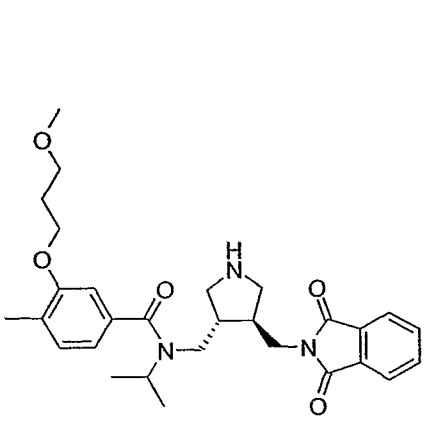
N-{(3S*,4S*)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-5-(3-methoxy-propoxy)-2-methyl-benzamide

2-Chloro-N-{(3S*,4S*)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-5-(3-methoxy-propoxy)-benzamide

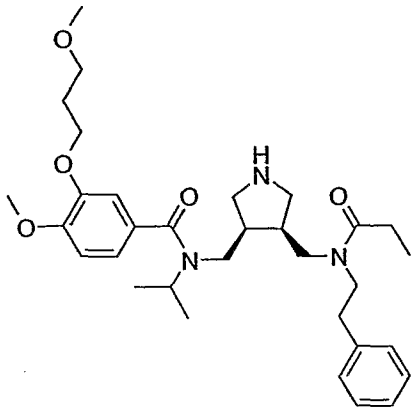
3-Chloro-N-{(3S*,4S*)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-5-(3-methoxy-propoxy)-benzamide
4-Chloro-N-{(3S*,4S*)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-3-(3-methoxy-propoxy)-benzamide
4-tert-Butyl-N-isopropyl-3-(3-methoxy-propoxy)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide
N-Isopropyl-4-methoxy-3-(2-methoxy-ethoxymethyl)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide
N-Isopropyl-3-(2-methoxy-ethoxymethyl)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-trifluoromethoxy-benzamide
N-Isopropyl-4-methoxy-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-3-(3,3,3-trifluoro-propoxy)-benzamide
N-Isopropyl-4-methoxy-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-3-(4,4,4-trifluoro-butoxy)-benzamide
N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-trifluoromethoxy-propoxy)-benzamide
N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-ethyl-N-isopropyl-3-(3-trifluoromethoxy-propoxy)-benzamide
N-Isopropyl-4-methoxy-3-(5-methyl-isoxazol-3-ylmethoxy)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide
N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-3-(2-methoxy-ethoxymethyl)-4-trifluoromethoxy-benzamide
3-(2-Ethoxy-ethoxy)-N-isopropyl-4-methoxy-N-{(3S,4S)-4-[(methyl-phenyl acetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[2-(4-methoxy-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

or a pharmaceutically acceptable salt thereof.

14. A compound of the formula



or



.

15. A compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 5 to 7 or 11 to 14 for use in the diagnostic or therapeutic treatment of a warm-blooded animal.

16. A compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 5 to 7 or 11 to 14 for use according to claim 16 in the treatment of a disease that depends on activity of renin, especially hypertension.

17. The use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 5 to 7 or 11 to 14 for the manufacture of a pharmaceutical composition for the treatment of a disease that depends on activity of renin, especially hypertension.

18. The use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 5 to 7 or 11 to 14 for the treatment of a disease that depends on activity of renin, especially hypertension.

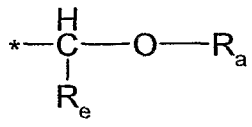
19. A pharmaceutical formulation, comprising a compound of the formula I, or a pharmaceutically acceptable salt thereof, as mentioned in any one of claims 1 to 4, 8 to 10 or preferably 5 to 7 or 11 to 14 and at least one pharmaceutically acceptable carrier material.

20. A method of treatment a disease that depends on activity of renin, comprising administering to a warm-blooded animal, especially a human, in need of such treatment a

pharmaceutically effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, as mentioned in any one of claims 1 to 14 or 15 or 16 or 18.

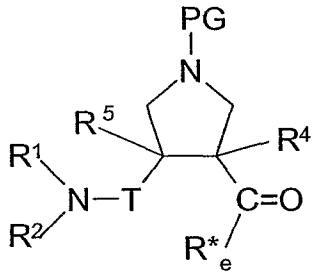
21. A process for the manufacture of a compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claim 4, comprising

(A) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (a)



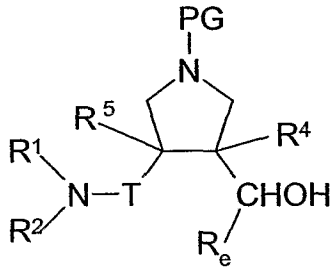
(a)

wherein R_a and R_e are as defined for a compound of the formula I and R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reducing a compound of the formula II,



(II)

wherein R^1, R^2, R^4, R^5 and T are as just defined, R^*_e is hydroxy or etherified hydroxyl such as OMe or R_e as defined for a compound of the formula I and PG is a protecting group, to the corresponding hydroxy compound of the formula III,



(III)

wherein R_e is as defined for a compound of the formula I and the other moieties are as defined, which is then either deprotected to a corresponding compound of the formula I wherein R_a in the moiety of the formula (a) is hydrogen or further reacted either

(i) with a compound of the formula IV,

$$R_a^*\text{-}X \qquad \text{(IV)}$$

wherein R_a^* is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-

alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or acyl and X is a leaving group, or

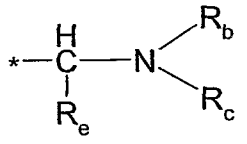
(ii) in order to introduce a moiety R_a which is N-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl or unsubstituted or substituted alkyl)-aminocarbonyl, with an isocyanato compound of the formula IV* or a chlorocarbamate of the formula $(R_a{}^{**})_2$-N-C(=O)-Cl,

$$R_a{}^{**}\text{-N=C=O} \qquad \text{(IV*)}$$

wherein $R_a{}^{**}$ is unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl or unsubstituted or substituted alkyl,

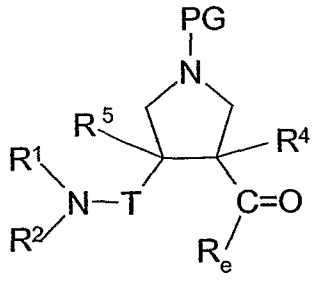
where reaction (i) or (ii) is followed by removal of any protecting group(s) to give a corresponding compound of the formula I if no further conversion requiring the presence of protecting groups is desired; or

(B) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (b)



(b)

wherein R_e, R_b and R_c are as defined for a compound of the formula I, and wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reacting an aldehyde compound of the formula V,



(V)

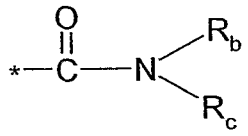
wherein R_e, R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group,

under conditions of reductive amination with a compound of the formula VI,

R_b-NH-R_c (VI)

wherein R_b and R_c are as defined for a compound of the formula I, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

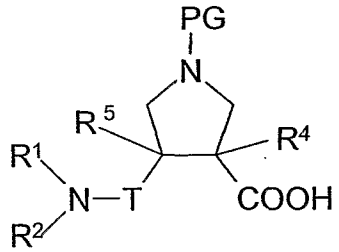
(C) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (f)



(f)

wherein R_b and R_c as well as R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I,

condensing an acid of the formula IIB,



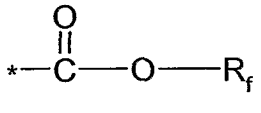
(IIB)

wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group, or a reactive derivative thereof, with an amine of the formula VI,

R_b-NH-R_c (VI)

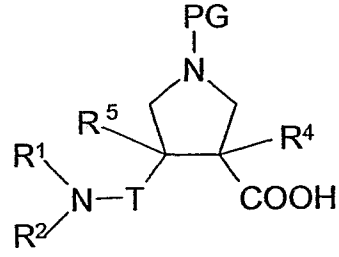
wherein R_b and R_c are as defined for a compound of the formula I, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

(D) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (g)



(g)

wherein R_f is as defined for a compound of the formula I and wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reacting an acid of the formula IIB,



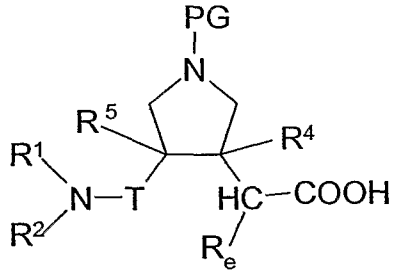
(IIB)

wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group, or a reactive derivative thereof, with an alcohol or alcohol derivative of the formula VII,

$$R_f\text{-}X \qquad \text{(VII)}$$

wherein R_f is as defined for a compound of the formula I and X is hydroxy or a leaving group, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

(E) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (d) or (e) as defined for a compound of the formula I and R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reacting a compound of the formula IIA,



(IIA)

wherein R^1, R^2, R^4, R^5, T and R_e are as defined for a compound of the formula I,

(i) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (d) with a compound of the formula VI,

$$R_b\text{-}NH\text{-}R_c \qquad \text{(VI)}$$

wherein R_a and R_b are as defined for a compound of the formula I, or

(ii) for the synthesis of a compound of the formula I wherein $R^3$is a moiety of the formula (e) with a compound of the formula VII,

$$R_f\text{-}X \qquad \text{(VII)};$$

wherein R_f is as defined for a compound of the formula I and X is hydroxy or a leaving group;

and, if desired, subsequent to any one or more of the processes (A), (B), (C), (D) or (E) mentioned above, converting an obtainable compound of the formula I or a protected form thereof into a different compound of the formula I, converting a salt of an obtainable compound of formula I into the free compound or a different salt, converting an obtainable free compound of formula I into a salt thereof, and/or separating an obtainable mixture of isomers of a compound of formula I into individual isomers;

where in any of the starting materials (especially of the formulae II to VIII), in addition to specific protecting groups mentioned, further protecting groups may be present, and any protecting groups are removed at an appropriate stage in order to obtain a corresponding compound of the formula I, or a salt thereof.