

**TETRAHYDROCARBAZOLE DERIVATIVES AS LIGANDS FOR G-
PROTEIN COUPLED RECEPTORS (GPCR)**

The present invention relates to novel tetrahydro-
5 carbazole derivatives which are ligands of G-protein
coupled receptors, and especially antagonists of
gonadotropin-releasing hormone, to the preparation
thereof, to the use thereof, and to the pharmaceutical
10 compositions which include these tetrahydrocarbazole
derivatives. The present invention also relates to a
method for treating pathological states mediated by G-
protein coupled receptors in a mammal, in particular a
human.

15 **Technical background**

The structural element which is common to all members
of the family of G-protein coupled receptors (GPCR) is
the presence of seven transmembrane alpha-helical
20 segments which are connected together by alternating
intra- and extracellular loops, with the amino terminus
being located on the extracellular side and the carboxy
terminus being located on the intracellular side. The
family of GPCRs can be divided into a plurality of
25 subfamilies (essentially family A, B and C) with
further sequence homologies within these subfamilies.
Since GPCRs are mainly involved in signal reception and
transduction, a large number of physiological functions
are influenced by them. GPCR ligands are therefore
30 potentially suitable as medicaments for the therapy and
prophylaxis of a large number of pathological states. A
brief survey of diseases which can be treated with GPCR
ligands is given in S. Wilson et al., *Pharmaceutical
News* 2000, 7(3) in Table 1.

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The majority of known GPCR ligands has a peptide
structure. However, peptide receptor ligands frequently
have some serious disadvantages such as, for example,

low bioavailability and metabolic instability. This is why there has recently been an intensified search for ligands in the form of small, non-peptide molecules. A special part is played in the search for novel, non-peptide receptor ligands by so-called "privileged structures". These "privileged structures" are the basic molecular structures which provide ligands for a large number of different receptors. The term "privileged structures" was used for the first time by Evans et al. in connection with benzodiazepine-based CCK (cholecystokinin) A antagonists from the natural product asperlicin (B.E. Evans et al., *J. Med. Chem.* 1988, 31, 2235). For proteases for example it has been known for some time that certain structural classes can serve as inhibitors of various enzymes. Whereas descriptions in the past were in particular of mechanism-based inhibitors of various proteases, however, more recently the frequency of examples of compounds which, by reason of their three-dimensional structure, fit well into the active binding region of various enzymes has increased (cf. M. Whittaker, *Cur. Opin. Chem. Biol.* 1998, 2, 386; A.S. Ripka et al., *ibid.*, 441). Such "privileged structures" have already been described for GPCRs too. Examples thereof are, besides the aforementioned benzodiazepines, also peptoids, 4-substituted 4-arylpiperidines, but also specific rigidized β -turn mimetics (B.A. Bunin et al., *Ann. Rep. Med. Chem.* 1999, 34, 267; R.N. Zuckermann et al., *J. Med. Chem.* 1994, 37, 2678; G.C.B. Harriman, *Tetrahedron Lett.* 2000, 41, 8853). A review of this is to be found in A.A. Patchett et al., *Ann. Rep. Med. Chem.* 1999, 35, 289. The tetrahydrocarbazole derivatives of the present invention provide a further class of "privileged structures" for GPCRs.

Although the present invention provides ligands for GPCRs in general, the compounds provided by the present invention are suitable in particular as ligands for a particular representative of the class of GPCRs, namely

gonadotropin-releasing hormone (GnRH). GnRH can be assigned to subfamily A of GPCRs (cf. U. Gether et al., *Endocrine Reviews* 2000, 21(1), 90).

5 GnRH is a hormone which is synthesized predominantly, but not exclusively, in mammals by nerve cells of the hypothalamus, is transported via the portal vein into the pituitary and is delivered in a controlled manner to the gonadotrophic cells. Interaction of GnRH with
10 its receptor having seven transmembrane domains stimulates the production and release of gonadotropic hormones by means of the second messenger inositol 1,4,5-trisphosphate and Ca^{2+} ions. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are
15 gonadotropins released by GnRH, stimulate the production of sex steroids and gamete maturation in both sexes. In addition to GnRH (also referred to as GnRH1), there are two further forms of GnRH, namely GnRH2 and 3.

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The GnRH receptor is used as pharmacological target in a number of disorders which depend on functioning sex hormone production, for example prostate cancer, premenopausal breast cancer, endometriosis and uterine
25 fibroids. GnRH superagonists or antagonists can be employed successfully for these disorders. A further possible indication is, in particular, male fertility control in combination with a replacement dose of androgens.

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One advantage of GnRH antagonists compared with GnRH superagonists is their direct activity in blocking gonadotropin secretion. Superagonists initially bring about overstimulation of the pituitary, leading to
35 increased gonadotropin release and sex steroid release. This hormonal response is terminated only after a certain delay on the basis of desensitization and downregulation of GnRH receptor concentrations. It is therefore possible that GnRH superagonists, both alone

and in combination with testosterone, are unable effectively to suppress sperm production in men and are thus unsuitable for male fertility control. In contrast to this, peptide GnRH antagonists, especially in
5 combination with a replacement dose of androgen, are able to induce a significant oligozoospermia in humans.

However, peptide GnRH antagonists have a number of disadvantages. Thus, they have a considerably lower
10 activity as superagonists and must accordingly be administered in considerably higher dosages. In addition, their oral bioavailability is low, so that they must be administered by injection. Repeated injections in turn lead to a reduction in compliance.
15 Furthermore, the synthesis of peptide GnRH antagonists is complicated and costly by comparison with non-peptide compounds.

Quinoline derivatives are disclosed as non-peptide GnRH
20 antagonists for example in WO 97/14682. However, it has not been possible to date to put any non-peptide GnRH antagonists on the market.

Technical problem

25 The problem on which the present invention is based is to provide novel compounds which are suitable for the treatment of GPCR-mediated pathological states and display in particular a GnRH-inhibiting (GnRH-
30 antagonistic) effect. The novel GPCR ligands, preferably GnRH antagonists, ought where possible to be superior to known peptide compounds and represent an effective alternative or improvement in relation to known non-peptide compounds. The novel GPCR ligands,
35 especially GnRH antagonists, should in particular have high activity and, where possible, a high oral bioavailability. Their synthesis ought moreover to be possible simply and at minimal cost. The present invention also provides pharmaceutical compositions

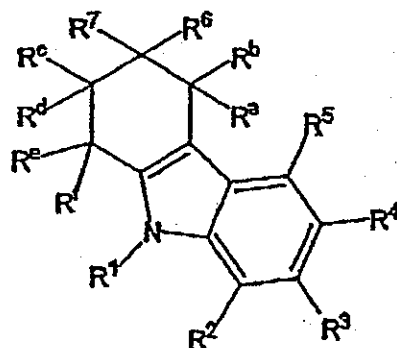
comprising the novel non-peptide GPCR ligands, in particular GnRH antagonists.

- 5 A further problem on which the present invention is based is to provide novel GPCR ligands, preferably GnRH antagonists, for use as pharmaceutical remedy and for use for producing pharmaceutical remedies, comprising the GPCR ligands, preferably GnRH antagonists.
- 10 In addition, it is an object of the present invention to provide a method for the treatment of GPCR-mediated pathological states, in particular for inhibiting GnRH, in a mammal, in particular a human.
- 15 All these problems are surprisingly solved by the provision of the novel tetrahydrocarbazole derivatives, of the pharmaceutical compositions which comprise these tetrahydrocarbazole derivatives, of the method for preparing these tetrahydrocarbazole derivatives, and of
- 20 the method for the treatment of GPCR-mediated pathological states, preferably for inhibition of GnRH, in a mammal, in particular a human, through administration of the tetrahydrocarbazole derivatives or the use of the tetrahydrocarbazole derivatives for
- 25 producing pharmaceutical remedies for the treatment of GPCR-mediated pathological states, in particular for GnRH inhibition.

Summary of the invention

Disclosed herein are novel tetrahydrocarbazole derivatives of the general formula (I).

In a first aspect of the present invention, there is provided a compound of the general formula (I)



(I)

in which

the radical R¹ is a hydrogen atom, a C₂-C₆ alkenyl or a C₁-C₆ alkyl radical and may optionally be substituted by an aryl, hetaryl radical or the group -COOR¹¹, where the aryl or hetaryl radical may be substituted by up to three substituents which are selected independently of one another from the group consisting of -NO₂, -CH₃, -CF₃, -OCH₃, -OCF₃ and halogen atoms, and

the radical R¹¹ is a hydrogen atom, a C₁-C₁₂ alkyl, a C₁-C₁₂ aralkyl, an aryl, hetaryl radical or the group -COCH₃ and may optionally be substituted by one substituent selected from the group consisting of -CONH₂, -COCH₃, -COOCH₃, -SO₂CH₃ and aryl radicals;

the radicals R², R³, R⁴ and R⁵ are each independently of one another a hydrogen atom, a halogen atom, the group -COOH, -CONH₂, -CF₃, -OCF₃, -NO₂, -CN, a C₁-C₆ alkyl, a C₁-C₆ alkenyl, a C₁-C₆

alkoxy, a C₁-C₁₂ aralkyl, an aryl or hetaryl radical;

5 the radical R₆ is the group -CONR⁸R⁹, -COOR⁸, -CH₂NR⁸R⁹, -CH₂R⁸, -CH₂OR⁸ or a C₁-C₁₂ alkenyl radical which is optionally substituted by the radicals R⁸ and R⁹,

10 where the radicals R⁸ and R⁹ are each independently of one another a hydrogen atom, a C₁-C₁₂ alkyl, a C₁-C₁₂ aralkyl, a C₁-C₁₂ hetaralkyl, an aryl or hetaryl radical, each of which may be substituted by one or more substituents selected from the group consisting of -OH, -NH₂, -CONHR¹⁰, -COOR¹⁰, -NH-C(=NH)-NH₂ and halogen atoms,

15 where the radical R¹⁰ is a hydrogen atom, a C₁-C₁₂ alkyl, a C₁-C₁₂ aralkyl, an aryl or hetaryl radical and is optionally substituted by the group -CON(R¹¹)₂,

20 or where the radicals R⁸ and R⁹ may together form a cyclic structure which consists either exclusively of carbon atoms or a combination of carbon atoms and heteroatoms;

25 the radical R⁷ is a hydrogen atom, a C₁-C₁₂ alkyl, a C₁-C₁₂ alkenyl, a C₁-C₁₂ aralkyl, an aryl or hetaryl radical, the group -NR¹²R¹³, -NHCOR¹⁴, -NHCONHR¹⁴, -NHCOOR¹⁴ or -NHSO₂R¹⁴ and may optionally be substituted by one or more substituents selected from the group consisting of -OH, -NH₂, -CONH₂, -COOH and halogen atoms,

30 the radicals R¹² and R¹³ are each independently of one another a hydrogen atom, a C₂-C₆ alkenyl or a C₁-C₁₂ alkyl radical and may optionally be substituted by one or more aryl or hetaryl radicals which in turn may be substituted by up to three substituents selected independently of one another from the group consisting of -NO₂, -CH₃, -CF₃, -OCH₃, -OCF₃ and halogen atoms,

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and the radical R^{14} is a hydrogen atom, a C_1 - C_{12} alkyl, a C_1 - C_{12} alkenyl, a C_1 - C_{12} aralkyl, an aryl or hetaryl radical which may optionally be substituted by one or more substituents selected from the group consisting of $-NO_2$, $-CH_3$, $-OR^{11}$, $-CF_3$, $-OCF_3$, $-OH$, $-N(R^{11})_2$, $-OCOR^{11}$, $-COOH$, $-CONH_2$, $-NHCONHR^{11}$, $-NHCOOR^{11}$ and halogen atoms;

and the radicals R^a , R^b , R^c , R^d , R^e and R^f are each independently of one another a hydrogen atom, a halogen atom, the group $-COOH$, $-CONH_2$, $-CF_3$, $-OCF_3$, $-NO_2$, $-CN$, a C_1 - C_6 alkyl, C_1 - C_6 alkoxy, an aryl or hetaryl radical;

with the proviso that the compound of the general formula (I) is not selected from the group consisting of 3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-amino-6-benzyloxy-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, methyl 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylate, (-)-menthyl 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylate or 3-tert-butoxycarbonylamino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid.

In a second aspect, pharmaceutical compositions which comprise at least one of the novel tetrahydrocarbazole derivatives of the general formula (I) are provided.

In a third aspect, the present invention provides tetrahydrocarbazole derivatives of the general formula (I) for use in therapy.

5 In a fourth aspect of the present invention, there is provided a method for preparing a compound of formula (I) as defined above, which comprises:

10 a) producing a compound of formula (I) in which R^1 is hydrogen by condensing a suitably substituted cyclohexanone derivative with a suitably substituted phenylhydrazine derivative or a salt thereof;

15 b) producing a compound of formula (I) in which R^1 is hydrogen, by reacting a suitably substituted carboxylic acid and a suitably substituted amine component to give a suitably substituted carbamate group at either R^6 or R^7 ;

20 c) producing a compound of formula (I) in which R^1 is other than hydrogen by reacting an anion derived by deprotonating a compound of formula (I) in which R^1 is hydrogen with a compound of formula R^1-X , wherein R^1 has the same meaning as R^1 above, save that it does not
25 represent hydrogen, and X represents a leaving group;

d) producing a compound of formula (I) by eliminating a corresponding compound of formula (I) from a solid phase wherein the compound is bound to a solid phase by a
30 tether severing of which generates the group R^6 ; or

e) removing one or more protecting groups from a corresponding compound of formula (I) in protected form.

In a further aspect, the present invention relates to the use of a tetrahydrocarbazole derivative of the general formula (I) for manufacture of a medicament for the treatment of GPCR-mediated pathological states, in particular for inhibition of GnRH. The present invention
5 likewise relates to a method for the treatment of GPCR-mediated pathological states, in particular for inhibition of GnRH, in a mammal, preferably a human, where an effective amount of a compound of the invention
10 of the general formula (I) is administered to the mammal, preferably the human, requiring such a treatment.

In a fifth aspect of the present invention, there is
15 provided the use of a compound as defined above for the manufacture of a medicament for the treatment of pathological states mediated by G protein-coupled receptors.

20 In a sixth aspect of the present invention, there is provided the use of a compound as defined in the first aspect, but including the compounds specifically excluded in the first aspect, for the manufacture of a medicament for inhibiting gonadotropin-releasing
25 hormone.

In a seventh aspect of the present invention, there is provided a compound as defined in the first aspect, but including the compounds specifically excluded in the
30 first aspect, for use in male fertility control or for female contraception.

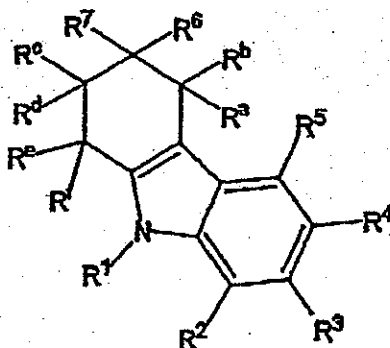
In an eighth aspect of the present invention, there is provided a pharmaceutical composition comprising at
35 least one compound as defined above.

The present invention additionally provides a method for preparing tetrahydrocarbazole derivatives of the general formula (I). This method comprises for example the steps of condensation of a cyclohexanone derivative, which is
5 tethered to a solid phase and is expediently substituted, with a suitably substituted phenylhydrazine derivative, a subsequent derivatization depending on the desired structure of the final compound, and finally elimination from the solid phase and isolation of the
10 product.

Detailed description of the invention

In a first aspect of the present invention there is
15 provision of novel tetrahydrocarbazole compounds of the general formula (I)

- 7 -



(I)

in which the radical R¹ is a hydrogen atom, a C₂-C₆ alkenyl or a C₁-C₆ alkyl radical and may optionally be substituted by an aryl, hetaryl radical or the group -COOR¹¹, where the aryl or hetaryl radical may be substituted by up to three substituents which are selected independently of one another from the group consisting of -NO₂, -CH₃, -CF₃, -OCH₃, -OCF₃ and halogen atoms, and

the radical R¹¹ is a hydrogen atom, a C₁-C₁₂ alkyl, a C₁-C₁₂ aralkyl, an aryl, hetaryl radical or the group -COCH₃ and may optionally be substituted by one substituent selected from the group consisting of -CONH₂, -COCH₃, -COOCH₃, -SO₂CH₃ and aryl radicals;

the radicals R², R³, R⁴ and R⁵ are each independently of one another a hydrogen atom, a halogen atom, the group -COOH, -CONH₂, -CF₃, -OCF₃, -NO₂, -CN, a C₁-C₆ alkyl, a C₁-C₆ alkenyl, a C₁-C₆ alkoxy, a C₁-C₁₂ aralkyl, an aryl or hetaryl radical;

the radical R⁶ is the group -CONR⁸R⁹, -COOR⁸, -CH₂NR⁸R⁹, -CH₂R⁸, -CH₂OR⁸ or a C₁-C₁₂ alkenyl radical which is optionally substituted by the radicals R⁸ and R⁹, where the radicals R⁸ and R⁹ are each independently of one another a hydrogen atom, a C₁-C₁₂ alkyl, a C₁-C₁₂ aralkyl, a C₁-C₁₂ hetaralkyl, an aryl or hetaryl radical, each of which may be substituted by one or

more substituents selected from the group consisting of -OH, -NH₂, -CONHR¹⁰, -COOR¹⁰, -NH-C(=NH)-NH₂ and halogen atoms,

where the radical R¹⁰ is a hydrogen atom, a C₁-C₁₂ alkyl, a C₁-C₁₂ aralkyl, an aryl or hetaryl radical and is optionally substituted by the group -CON(R¹¹)₂, or where the radicals R⁸ and R⁹ may together form a cyclic structure which consists either exclusively of carbon atoms or a combination of carbon atoms and heteroatoms;

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the radical R⁷ is a hydrogen atom, a C₁-C₁₂ alkyl, a C₁-C₁₂ alkenyl, a C₁-C₁₂ aralkyl, an aryl or hetaryl radical, the group -NR¹²R¹³, -NHCOR¹⁴, -NHCONHR¹⁴, -NHCOOR¹⁴ or -NHSO₂R¹⁴ and may optionally be substituted by one or more substituents selected from the group consisting of -OH, -NH₂, -CONH₂, -COOH and halogen atoms,

the radicals R¹² and R¹³ are each independently of one another a hydrogen atom, a C₂-C₆ alkenyl or a C₁-C₁₂ alkyl radical and may optionally be substituted by one or more aryl or hetaryl radicals which in turn may be substituted by up to three substituents selected independently of one another from the group consisting of -NO₂, -CH₃, -CF₃, -OCH₃, -OCF₃ and halogen atoms,

and the radical R¹⁴ is a hydrogen atom, a C₁-C₁₂ alkyl, a C₁-C₁₂ alkenyl, a C₁-C₁₂ aralkyl, an aryl or hetaryl radical which may optionally be substituted by one or more substituents selected from the group consisting of -NO₂, -CH₃, -OR¹¹, -CF₃, -OCF₃, -OH, -N(R¹¹)₂, -OCOR¹¹, -COOH, -CONH₂, -NHCONHR¹¹, -NHCOOR¹¹ and halogen atoms;

and the radicals R^a, R^b, R^c, R^d, R^e and R^f are each independently of one another a hydrogen atom, a halogen atom, the group -COOH, -CONH₂, -CF₃, -OCF₃, -NO₂, -CN, a C₁-C₆ alkyl, C₁-C₆ alkoxy, an aryl or hetaryl radical;

with the proviso that the compound of the general formula (I) is not selected from the group consisting of 3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic

acid, 3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-amino-6-benzyloxy-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, methyl 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylate, 5 (-)-menthyl 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylate or 3-tert-butoxycarbonylamino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid.

10 One embodiment of the invention are compounds of the general formula (I) as indicated above with all the meanings indicated above for the radicals contained in (I), where the radical R^{11} is a heteroalkyl or a hetarylalkyl radical.

15 The basic tetrahydrocarbazole structures of those compounds which are specifically excluded above from the compounds falling within the definition of the general formula (I) were introduced by Y. Maki et al. 20 in *Chem. Pharm. Bull.* 1973, 21 (11), 2460-2465 and by R. Millet et al. in *Letters in Peptide Science* 1999, 6, 221-233.

25 The terms indicated for explanation of the compounds of the general formula (I) have in particular the following meaning:

30 C_1-C_6 or C_1-C_{12} "alkyl radical" means a branched or unbranched, cyclic or acyclic, optionally substituted alkyl group having 1 to 6 or 1 to 12 carbon atoms, respectively. Representative examples of such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, n-heptyl, n- 35 octyl, n-nonyl, n-decyl, n-undecyl and n-dodecyl groups, and cyclic groups, in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl groups, 1-cyclopropyl-, 1-cyclobutyl-, 1-cyclopentyl-, 1-cyclohexyl-, 1-cycloheptylethyl-, 2-cyclopropyl-, 2-

cyclobutyl-, 2-cyclopentyl-, 2-cyclohexyl-, 2-cycloheptylethyl groups and the like, but are not restricted to these.

- 5 C₂-C₆ "alkenyl radical" means a branched or unbranched, cyclic or acyclic, optionally substituted, mono- or polyunsaturated alkenyl group having 2 to 6 carbon atoms. Representative examples of such alkenyl groups include vinyl, allyl, prop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, pent-1-enyl, pent-2-enyl, pent-3-enyl, pent-4-enyl, penta-1,3-dienyl, penta-1,4-dienyl, penta-2,3-dienyl, isoprenyl, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, hex-5-enyl, hexa-1,3-dienyl, hexa-1,4-dienyl, hexa-1,5-dienyl, hexa-2,4-dienyl, hexa-2,5-dienyl, hexa-1,4-dienyl, hexa-1,3,5-trienyl groups and the like, but are not restricted to these.

- C₂-C₆ "alkoxy radical" means a branched or unbranched, cyclic or acyclic, optionally substituted alkoxy group having 2 to 6 carbon atoms. Representative examples of such alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy, n-hexoxy, cyclohexyloxy groups and the like, but are not restricted to these.

- C₁-C₁₂ "aralkyl radical" means an alkyl radical having 1 to 12 carbon atoms which is substituted by one or more aryl radicals. Representative examples of such aralkyl groups for the purposes of the present invention include benzyl, 1-phenylethyl, 1-phenylpropyl, 1-phenylbutyl, 1-phenylhexyl, 1-phenyl-2-methylethyl, 1-phenyl-2-ethylethyl, 1-phenyl-2,2-dimethylethyl, benzhydryl, triphenylmethyl, 2- or 3-naphthylmethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl groups and the like, but are not restricted to these. Correspondingly, a "hetaralkyl radical" is an alkyl radical substituted by a heteroaryl radical.

"Aryl radical" means an optionally substituted mono- or polycyclic aromatic group. Representative examples of such aryl groups include phenyl, naphthyl groups and the like, but are not restricted to these.

The term "hetaryl radical" is identical with the term "heteroaryl radical" and represents an aryl group as defined above which includes in its structure one or more heteroatoms, in particular nitrogen, phosphorus, oxygen, sulfur and arsenic atoms. Representative examples of such hetaryl or heteroaryl groups include unsubstituted hetaryl radicals and substituted hetaryl radicals, in particular imidazolyl, pyridyl, quinolinyl groups and the like, but are not restricted to these.

The term "cyclic structure" includes optionally substituted mono- or polycyclic cyclic structures with a varying number of ring members, in particular five-, six- and seven-membered cyclic structures. These cyclic structures may include besides carbon atoms also one or more heteroatoms such as, in particular, nitrogen, phosphorus, oxygen, sulfur and arsenic atoms. The cyclic structures may include saturated, but also partially or completely unsaturated, structural elements. Representative examples of such cyclic structures include aza-, oxa-, thia-, phosphacyclopentane-, -cyclohexane-, -cycloheptane-, diaza-, dioxo-, dithia-, diphosphacyclopentane-, -cyclohexane, -cycloheptane basic cyclic structures and the like, and basic cyclic structures with mixed heteroatom exchange, but are not restricted to these.

"Halogen atoms" include in particular fluorine, chlorine, bromine and iodine atoms, particularly preferably chlorine atoms.

Reference may also be made at this point to the fact that, besides the compounds of the general formula (I),

as defined above, which are mentioned per se, the present invention also encompasses physiologically tolerated derivatives or analogs, especially also salts of these compounds.

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It may further be remarked at this point that the term "receptor ligand" or "ligand" is intended for the purposes of the present invention to designate any compound which binds in any manner to a receptor (in the present invention, the receptor is a GPCR receptor, preferably a GnRH receptor) and induces either an activation, inhibition or other conceivable effect on this receptor. The term "ligand" thus includes agonists, antagonists, partial agonists/antagonists and other ligands which elicit on the receptor an effect which resembles the effect of agonists, antagonists or partial agonists/antagonists. The compounds of the invention of the general formula (I) are preferably GnRH antagonists.

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One embodiment of the present invention are novel tetrahydrocarbazole derivatives of the invention of the general formula (I) in which the radical R^7 is not a hydrogen atom when the radical R^6 is at the same time an alkyl radical.

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A further embodiment of the present invention are compounds of the general formula (I) in which the radical R^7 is not in any case a hydrogen atom.

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Preferred novel tetrahydrocarbazole derivatives of the invention of the general formula (I) are those compounds in which the radicals R^a , R^b , R^c , R^d , R^e and R^f are hydrogen atoms.

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Likewise preferred novel tetrahydrocarbazole derivatives of the invention of the general formula (I) are those compounds in which the radical R^1 is a hydrogen atom.

Preferred novel tetrahydrocarbazole derivatives of the invention of the general formula (I) are additionally those compounds in which the radicals R^2 , R^3 , R^4 and/or R^5 are not hydrogen atoms. Particularly preferred compounds of the general formula (I) in this connection are those in which the radicals R^2 , R^3 , R^4 and R^5 are independently of one another methyl, chloro or methoxy radicals. Very particularly preferred compounds of the general formula (I) in this connection are those in which at least the radical R^2 is not a hydrogen atom, especially the compounds

phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-8-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (compound no. 150a in the examples)

phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6-chloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (148a),

phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (147a).

Preferred novel tetrahydrocarbazole derivatives of the invention of the general formula (I) are also those compounds in which R^6 is a hydrophobic radical which includes alkyl, aryl and/or hetaryl structures and which carries a hydrogen bond donor-acceptor system at a distance of from two to four single bonds, counting from the carbon atom substituted by the radicals R^6 and R^7 . Particularly preferred compounds of the general formula (I) are those where the radical R^6 is a phenylalanylamide residue, in particular the compound phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]amino]carbonyl]-2,3,4,9-

tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (66),

is an isoleucylamide residue, in particular the compound phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-

5 (aminocarbonyl)-2-methylbutyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (64),

is a valyl-4-aminobenzamide residue, in particular the compound phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-

10 [[4-(aminocarbonyl)phenyl]amino]carbonyl]-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (45),

is a valyl-N-methylamide residue, in particular the compound phenylmethyl [(1S,2S)-2-methyl-1-[[[(3R)-

15 2,3,4,9-tetrahydro-3-[[[(1S)-2-methyl-1-[(methylamino)-carbonyl]propyl]amino]carbonyl]-1H-carbazol-3-yl]amino]carbonyl]butyl]carbamate (222a),

is a methyloxymethyl-4-pyridyl radical, in particular the compound 2,3,4,9-tetrahydro-3-(3-phenylpropyl)-O-

20 (4-pyridinylmethyl)-1H-carbazole-3-methanol (287),

is a carboxyl radical, in particular the compound 2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazole-3-carboxylic acid (273),

or is an ethyl propenoate radical, in particular the

25 compound ethyl 3-[2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazol-3-yl]-2-propenoate (289).

Likewise particularly preferred are compounds of the general formula (I) in which the radical R⁶ is a

carbonylvalylamide residue, in particular the compound

30 phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (58),

is a carbonylthreonylamide residue, in particular the

35 compound phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2R)-1-(aminocarbonyl)-2-hydroxypropyl]amino]carbonyl]-

2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate,

is a cyclic carboxamide residue (such as, for example, a carbonylproplylamide radical, in particular the compound phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(2S)-2-(aminocarbonyl)-1-pyrrolidinyl]carbonyl]-2,3,4,9-tetra-
5 hydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (181a),
or a carbonyloctahydroindolyl-2-carboxamide residue, in particular the compound phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(2S)-2-(aminocarbonyl)octahydro-1H-indol-1-
10 yl]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (190a)),
is a 4-carboxamidophenylcarboxamide residue, in particular the compound phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[4-(aminocarbonyl)phenyl]amino]carbonyl]-
15 2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (62),
is a methylaminomethyl-2-pyridyl radical, in particular the compound 2,3,4,9-tetrahydro-3-(3-phenylpropyl)-N-(2-pyridinylmethyl)-1H-carbazole-3-methanamine (279),
20 is a carbonylvalinol residue, in particular the compounds phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methyl-
butyl]carbamate (267b)
25 and 2,3,4,9-tetrahydro-N-[(1S)-1-(hydroxymethyl)-2-methylpropyl]-3-(3-phenylpropyl)-1H-carbazole-3-carboxamide (276)
or is a methylvalinol residue, in particular the compound (2S)-3-methyl-2-[[[2,3,4,9-tetrahydro-3-(3-
30 phenylpropyl)-1H-carbazol-3-yl]methyl]amino]-1-butanol (284).

Preferred novel tetrahydrocarbazole derivatives of the invention of general formula (I) are also compounds in
35 which R⁷ is a hydrophobic radical comprising alkyl, aryl and/or hetaryl structures. Particular preference is given in this connection to compounds of the general formula (I) in which the radical R⁷ is a 2,3-biphenyl-propionylamino radical, in particular the compound

N-[[(3R)-2,3,4,9-tetrahydro-3-[(1-oxo-2,3-diphenylpropyl)amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide (18),

is an indanoylamino radical, in particular the compound

5 (3R)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-3-[[(2,3-dihydro-1H-inden-1-yl)carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide (162a),

is an indolylacetyl amino radical, in particular the compound

10 (3S)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1H-indol-3-ylacetyl)-amino]-1H-carbazole-3-carboxamide (164b),

is a 2-naphthylacetyl amino radical, in particular the compound

15 (3S)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(2-naphthalinylacetyl)-amino]-1H-carbazole-3-carboxamide (161b)

or is a 3-propionyl amino radical, in particular the compound

20 N-[[(3R)-2,3,4,9-tetrahydro-3-[[(2S,3S)-3-methyl-1-oxo-2-[(1-oxo-3-phenylpropyl)amino]pentyl]-amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide (22).

Likewise particularly preferred are compounds of the general formula (I) in which R⁷ is a phenylmethyl-carboxamide residue substituted on the aromatic system,

25 in particular the compounds (3R)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[(4-methylphenyl)acetyl]amino]-1H-carbazole-3-carboxamide (165a),

N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[(4-methoxyphenyl)-acetyl]amino]-1H-carbazole-3-carboxamide (175),

30 (3R)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-3-[[(3-bromophenyl)acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide (96),

(3R)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-3-[[(4-fluorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide (91),

35 (3R)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-3-[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide (167a),

is a phenylhexylamine residue, in particular the compound (3R)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(6-phenylhexyl)amino]-1H-carbazole-3-carboxamide (234a)

5 or is a phenylpropyl radical, in particular the compounds 6,8-dichloro-2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazole-3-carboxylic acid (275) and ethyl 6,8-dichloro-2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazole-3-carboxylate (272).

10

Also preferred are those novel compounds of the invention of the general formula (I) which are in the R configuration at the carbon atom substituted by the radicals R^6 and R^7 when the radicals R^6 and R^7 together
15 form an alpha-amino carboxylic acid structural element.

Most preferred for the purposes of the present invention are the compounds phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]-amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate (184a), phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methyl-
20 butyl]carbamate (267a), (2S)-1-[[[(3R)-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-yl]carbonyl]-2-pyrrolidinecarboxamide (189a) and 6,8-dichloro-2,3,4,9-tetrahydro-3-(3-phenylpropyl)-N-(2-pyridinylmethyl)-1H-carbazole-3-methanamine (283).

30

Further representatives of novel compounds of the invention of the general formula (I), including their preparation, are indicated in the examples.

35 The novel tetrahydrocarbazole derivatives (I) of the invention, as defined above, are ligands of GPCR and can be employed in particular for the inhibition, i.e. as antagonists, of gonadotropin-releasing hormone for example for male fertility control, for hormone

therapy, for the treatment of female sub- or infertility, for female contraception and for tumor control.

- 5 In male fertility control, the compounds of the invention bring about a reduction in spermatogenesis. Combined administration with androgens, e.g. testosterone or testosterone derivatives such as, for example, testosterone esters, is preferred. The
10 testosterone derivatives can in this case be administered for example by injection, e.g. by intramuscular depot injection.

The compounds (I) of the invention can also be employed
15 where appropriate in combination with other hormones, e.g. estrogens or/and progestins, in hormone therapy, for example for the treatment of endometriosis, uterine leiomyomas and uterine fibroids. Combinations of the GnRH antagonists of the invention and tissue-selective
20 partial estrogen agonists such as Raloxifen[®] are particularly preferred. In addition, the compounds of the invention can be employed in hormone replacement therapy. The compounds (I) of the invention can moreover be employed to increase female fertility, for
25 example by inducing ovulation, and for the treatment of sterility.

On the other hand, the novel compounds (I) of the invention are also suitable for contraception in women.
30 Thus, the GnRH antagonist of the invention can be administered on days 1 to 15 of the cycle together with estrogen, preferably with very small estrogen dosages. On days 16 to 21 of the cycle of intake, progestagen is added to the estrogen/GnRH antagonist combination. The
35 GnRH antagonist of the invention can be administered continuously throughout the cycle. It is possible in this way to reduce the hormone dosages and thus achieve a reduction in the side effects of nonphysiological hormone levels. It is additionally possible to achieve

advantageous effects in women suffering from polycystic ovary syndrome and androgen-dependent disorders such as acne, seborrhea and hirsutism. An improved control of the cycle by comparison with previous administration methods is also to be expected. Further indications are benign prostate hyperplasia, gonadal protection during chemotherapy, controlled ovary stimulation/assisted reproduction techniques, infantile development disorders, e.g. precocious puberty and polycystic ovaries.

Finally, the compounds (I) of the invention, as defined above, can also be employed for the treatment of hormone-dependent neoplastic diseases such as premenopausal cancer, prostate cancer, ovarian cancer and endometrial cancer, by suppressing endogenous sex steroid hormones.

The novel compounds (I) of the invention, as defined above, are, as GPCR ligands, in particular GnRH antagonists, suitable for the treatment of the pathological states detailed above for administration to mammals, in particular humans, but also for veterinary medical purposes, e.g. in pets and productive livestock, but also in wild animals.

Administration is possible in a known manner, for example orally or non-orally, in particular topically, rectally, intravaginally, nasally or by injection or implantation. Oral administration is preferred. The novel compounds (I) of the invention are converted into a form capable of administration and, where appropriate, mixed with pharmaceutically acceptable carriers or diluents. Suitable excipients and carriers are described for example in *Ullman's Encyclopedia of Technical Chemistry*, Vol. 4 (1953), 1-39; *Journal of Pharmaceutical Sciences*, Vol. 52 (1963), 918 ff; H. v. Czetsch-Lindenwald, "Hilfsstoffe für Pharmazie und angrenzende Gebiete", *Pharm. Ind.* 2, 1961, 72ff;

Dr. H.P. Fiedler, "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Cantor KG, Aulendorf in Württemberg, 1971.

5 Oral administration can take place for example in solid form as tablet, capsule, gel capsule, coated tablet, granulation or powder, but also in the form of a drinkable solution. For oral administration, the novel compounds of the invention of the general formula (I),
10 as defined above, can be combined with known and conventionally used, physiologically tolerated excipients and carriers such as, for example, gum arabic, talc, starch, sugars such as, for example, mannitol, methylcellulose, lactose, gelatin, surface-
15 active agents, magnesium stearate, cyclodextrins, aqueous or nonaqueous carriers, diluents, dispersants, emulsifiers, lubricants, preservatives and flavors (e.g. essential oils). The compounds of the invention can also be dispersed in a microparticulate, e.g. nano-
20 particulate, composition.

Non-oral administration can take place for example by intravenous, subcutaneous or intramuscular injection of sterile aqueous or oily solutions, suspensions or
25 emulsions, by means of implants or by ointments, creams or suppositories. Administration as extended-release form is also possible where appropriate. Implants may contain inert materials, e.g. biodegradable polymers or synthetic silicones such as, for example, silicone
30 rubber. Intravaginal administration is possible for example by means of pessaries. Intrauterine administration is possible for example by means of diaphragms, etc. In addition, transdermal administration, in particular by means of a formulation
35 suitable for this purpose and/or suitable means such as, for example, patches, is also provided.

As already explained above, the novel compounds (I) of the invention can also be combined with other active

pharmaceutical ingredients. During a combination therapy, the individual active ingredients can be administered simultaneously or separately, in particular either by the same route (e.g. orally) or by
5 separate routes (e.g. orally and as injection). They may be present and administered in identical or different amounts in a unit dose. It is also possible to apply a particular dosage regimen where this appears expedient. It is also possible in this way to combine a
10 plurality of the novel compounds (I) of the invention together.

The dosage may vary within a wide range depending on the nature of the indication, the severity of the
15 disorder, the mode of administration, the age, sex, body weight and sensitivity of the subject to be treated. It is within the abilities of a skilled worker to determine a "pharmacologically effective amount" of the combined pharmaceutical composition. Unit doses of
20 from 1 μ g to 100 mg, particularly preferably from 1 μ g to 10 mg and most preferably from 1 μ g to 1 mg, per kg of body weight of the subject to be treated are preferred. Administration can take place in a single dose or a plurality of separate dosages.

25 In a further aspect of the present invention, accordingly, the present invention also encompasses pharmaceutical compositions as described above, comprising at least one of the novel compounds (I) of
30 the invention, as defined above, and where appropriate pharmaceutically acceptable carriers and/or excipients. Preferred and particularly preferred pharmaceutical compositions are those comprising at least one of the aforementioned preferred or particularly preferred
35 novel compounds (I) of the invention, in particular the compounds mentioned by name above. In pharmaceutical compositions according to the present invention it is possible, besides the at least one compound of the general formula (I), as defined above, for other active

pharmaceutical ingredients also to be present, as already described in detail above.

At least one of the novel compounds (I) of the invention, as defined above, is present in the pharmaceutical compositions of the invention in one of the unit doses mentioned above as preferred, particularly preferred or most preferred, specifically and preferably in an administration form which makes oral administration possible.

In addition, in a further aspect, the present invention provides compounds of the general formula (I) as defined above for use in therapy.

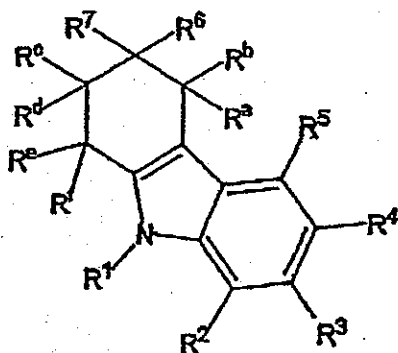
Preferred tetrahydrocarbazole compound of the invention of the general formula (I), as defined above, for use in therapy are in turn those compounds mentioned above as preferred and particularly preferred compounds, in particular the preferred compounds of the invention mentioned by name, and the compounds mentioned in the examples.

Concerning pharmaceutical compositions comprising compounds (I) of the invention, and concerning compounds (I) of the invention for use in therapy, reference may be made in relation to the possibilities for use and administration to what has already been said concerning the novel compounds (I) of the invention, as defined above.

In another aspect, the present invention also provides the use of at least one tetrahydrocarbazole derivative of the invention of the general formula (I), as defined above, with - as defined at the outset - the tetrahydrocarbazoles disclosed in the publications by Millet et al. and Maki et al. being excluded from the meaning of the general formula (I), for the manufacture of a

medicament for the treatment of GPCR-mediated diseases, in particular for inhibition of gonadotropin-releasing hormone (GnRH).

- 5 In addition, the present invention provides in a further aspect the use of at least one compound of the invention of the general formula (I) as defined above, but including the compounds previously excluded by name from the publications of Millet et al. and Maki et al.,
10 namely 3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-amino-6-benzyloxy-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, methyl 3-
15 acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylate, (-)-menthyl 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylate and 3-tert-butoxycarbonylamino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, for the manufacture of a medicament for inhibiting GnRH,
20 preferably for male fertility control, for hormone therapy, for the treatment of female sub- and infertility, for female contraception and for tumor control. Stated more clearly, the term "a compound of the general formula (I) as defined above, but
25 including the compounds excluded above by name" means a compound of the general formula (I)



- in which the radical R^1 is a hydrogen atom, a $C_2 - C_6$ alkenyl or a $C_1 - C_6$ alkyl radical and may optionally be substituted by an aryl, hetaryl radical or the group $-COOR^{11}$, where the aryl or hetaryl radical may be substituted by up to three substituents which are selected independently of one another from the group consisting of $-NO_2$, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$ and halogen atoms, and
- the radical R^{11} is a hydrogen atom, a $C_1 - C_{12}$ alkyl, a $C_1 - C_{12}$ aralkyl, an aryl, hetaryl radical or the group $-COCH_3$ and may optionally be substituted by one substituent selected from the group consisting of $-CONH_2$, $-COCH_3$, $-COOCH_3$, $-SO_2CH_3$ and aryl radicals;
- the radicals R^2 , R^3 , R^4 and R^5 are each independently of one another a hydrogen atom, a halogen atom, the group $-COOH$, $-CONH_2$, $-CF_3$, $-OCF_3$, $-NO_2$, $-CN$, a $C_1 - C_6$ alkyl, a $C_1 - C_6$ alkenyl, a $C_1 - C_6$ alkoxy, a $C_1 - C_{12}$ aralkyl, an aryl or hetaryl radical;
- the radical R^6 is the group $-CONR^8R^9$, $-COOR^8$, $-CH_2NR^8R^9$, $-CH_2R^8$, $-CH_2OR^8$ or a $C_1 - C_{12}$ alkenyl radical which is optionally substituted by the radicals R^8 and R^9 , where the radicals R^8 and R^9 are each independently of one another a hydrogen atom, a $C_1 - C_{12}$ alkyl, a $C_1 - C_{12}$ aralkyl, a $C_1 - C_{12}$ hetaralkyl, an aryl or hetaryl radical, each of which may be substituted by one or more substituents selected from the group consisting of $-OH$, $-NH_2$, $-CONHR^{10}$, $-COOR^{10}$, $-NH-C(=NH)-NH_2$ and halogen atoms,
- where the radical R^{10} is a hydrogen atom, a $C_1 - C_{12}$ alkyl, a $C_1 - C_{12}$ aralkyl, an aryl or hetaryl radical and is optionally substituted by the group $-CON(R^{11})_2$, or where the radicals R^8 and R^9 may together form a cyclic structure which consists however exclusively of carbon atoms or a combination of carbon atoms and heteroatoms;

the radical R^7 is a hydrogen atom, a $C_1 - C_{12}$ alkyl, a $C_1 - C_{12}$ alkenyl, a $C_1 - C_{12}$ aralkyl, an aryl or hetaryl radical, the group $-NR^{12}R^{13}$, $-NHCOR^{14}$, $-NHCONHR^{14}$, $-NHCOOR^{14}$ or $-NHSO_2R^{14}$ and may optionally be substituted
5 by one or more substituents selected from the group consisting of $-OH$, $-NH_2$, $-CONH_2$, $-COOH$ and halogen atoms,
the radicals R^{12} and R^{13} are each independently of one another a hydrogen atom, a $C_2 - C_6$ alkenyl or a $C_1 - C_{12}$
10 alkyl radical and may optionally be substituted by one or more aryl or hetaryl radicals which in turn may be substituted by up to three substituents selected independently of one another from the group consisting of $-NO_2$, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$ and halogen atoms,
15 and the radical R^{14} is a hydrogen atom, a $C_1 - C_{12}$ alkyl, a $C_1 - C_{12}$ alkenyl, a $C_1 - C_{12}$ aralkyl, an aryl or hetaryl radical which may optionally be substituted by one or more substituents selected from the group consisting of $-NO_2$, $-CH_3$, $-OR^{11}$, $-CF_3$, $-OCF_3$, $-OH$,
20 $-N(R^{11})_2$, $-OCOR^{11}$, $-COOH$, $-CONH_2$, $-NHCONHR^{11}$, $-NHCOOR^{11}$ and halogen atoms;

and the radicals R^a , R^b , R^c , R^d , R^e and R^f are each independently of one another a hydrogen atom, a halogen
25 atom, the group $-COOH$, $-CONH_2$, $-CF_3$, $-OCF_3$, $-NO_2$, $-CN$, a $C_1 - C_6$ alkyl, a $C_1 - C_6$ alkoxy, an aryl or hetaryl radical.

The indications already mentioned in connection with
30 the novel compounds of the invention of the general formula (I), as defined above (i.e. excluding the compound disclosed in the publications of Maki et al. and Millet et al. and mentioned above by name) have already been given above in relation to the novel
35 compounds (I) of the invention. The compounds which are preferred and particularly preferred in the use of the compounds just defined for the manufacture of a medicament for inhibiting GnRH are identical to the preferred and particularly preferred compounds already

mentioned above in connection with the novel compounds of the invention of the general formula (I), as defined above.

5 The present invention provides in a further aspect the use of a compound (I) of the invention as defined above, but likewise including the compounds excluded by name at the outset, for male fertility control or for female contraception. Preferred and particularly
10 preferred compounds of the invention for this use are those compounds already mentioned at the outset as preferred or particularly preferred compounds of the invention of general formula (I) as defined above.

15 In addition, the present invention provides a method for male fertility control or for female contraception, comprising the administration of an amount, effective for male fertility control or for female contraception, of a compound of the invention as defined in the
20 immediately preceding paragraph, to a subject, preferably a mammal, particularly preferably a human.

In another aspect, the present invention relates to a method for the treatment of pathological states
25 mediated by GPCR. The method comprises the administration of at least one compound (I) of the invention, as defined above, to a mammal, in particular a human, when such a treatment is necessary. The administration normally takes place in a
30 pharmaceutically effective amount. As already explained above in relation to the novel compounds (I) of the invention and the pharmaceutical compositions of the invention, it is the task of the expert knowledge of a skilled worker to determine a pharmaceutically
35 effective amount, depending on the specific requirements of the individual case. However, the compounds (I) of the invention are preferably administered in a unit dose of from 1 μ g to 100 mg, particularly preferably from 1 μ g to 10 mg and most

preferably from 1 μ g to 1 mg per body weight of subject to be treated. The preferred administration form is oral administration. The administration of one or more of the compounds (I) of the invention in combination with at least one further active ingredient, as already explained above, is also provided.

In addition, the present invention also relates to a method for inhibiting GnRH in a patient, comprising administration of a pharmaceutically effective amount of a compound of the general formula (I), as defined above, but including compounds excluded by name above, to a patient requiring such a treatment. The method is preferably used in male fertility control, hormone therapy, female contraception, treatment of female sub- or infertility and tumor control.

Finally, the present invention provides in a last aspect also a method for the production of the novel tetrahydrocarbazole derivatives of the invention of the general formula (I). The method for the preparation of the compounds of the invention of the general formula (I) can be carried out in various ways, e.g. in liquid phase or as partial or complete solid-phase synthesis. The choice of the suitable synthesis conditions for preparing individual representatives of compounds of the general formula (I) can be made by a skilled worker on the basis of his common general knowledge. One method of the invention for the preparation of compounds of the invention of the general formula (I) is firstly described generally below. A specific variant of the method, namely a solid-phase method, is then described. For further illustration of the present invention, the examples listed thereafter include numerous representatives of compounds of the general formula (I).

One method for the preparation of the compounds of the invention of the general formula (I) is preferably

carried out in the following way:

The central tetrahydrocarbazole structure can be obtained by a Fischer indole synthesis known per se. For this purpose, a suitably substituted cyclohexanone derivative provided where appropriate with protective groups is condensed with the phenylhydrazine derivative which is desired in each case and is likewise suitably substituted and provided where appropriate with protective groups (e.g. as described by Britten & Lockwood, *J.C.S. Perkin I* 1974, 1824 or as described by Maki et al., *Chem. Pharm. Bull.* 1973, 21, 240). In particular, the cyclohexanone structure is substituted in positions 3,3', 5,5' and 6,6' via the radicals R^a to R^f , and in positions 4,4' via the radicals, or where appropriate by precursors of the radicals, R^6 and R^7 . The phenylhydrazine structure is optionally substituted by the radicals R^2 to R^5 . Phenylhydrazine derivatives which are not commercially available can be prepared by methods known to the skilled worker. Positional isomers which result where appropriate in the condensation of the cyclohexanone derivative and the phenylhydrazine derivative can be separated by chromatographic methods such as, for example, HPLC.

After the synthesis of the central tetrahydrocarbazole structure, the radical R^1 can be introduced by N-alkylation of the nitrogen atom in position 9 with appropriate R^1 -halides with use of base (e.g. as described by Pecca & Albonico, *J. Med. Chem.* 1977, 20, 487 or else as described by Mooradian et al., *J. Med. Chem.* 1970, 13, 327).

The radicals R^6 and R^7 can, as already indicated above, be introduced in various ways depending on their nature, which is explained in detail below.

α -Aminocarboxylic acid structures in these radicals can be obtained by treating ketones with $NH_4(CO)_3$ and KCN

under Schotten-Baumann conditions known per se, and subsequent alkaline hydrolysis of the hydantoin which is formed (Britten & Lockwood, *J.C.S. Perkin I* 1974, 1824).

5

Amide residues are preferably generated using methods known per se from peptide chemistry. For this purpose, the acid component is activated with an activating reagent such as DCC or else HATU (*Tetrahedron Lett.* 1994, 35, 2279) and condensed in the presence of a base such as DIPEA and/or DMAP with the amino component.

10

Ester residues can also be obtained by using the desired alcohols under analogous conditions. The solvent used in this case is preferably anhydrous.

15

Secondary or tertiary amide residues are obtained from primary amines either by nucleophilic substitution of alkyl halides or by reductive amination of aldehydes/ ketones (e.g. *J. Org. Chem.* 1996, 61, 3849 or *Synth. Comm.* 1994, 609).

20

Sulfonamide residues are obtained from the corresponding amides by reaction with sulfonyl chlorides.

25

Urea residues are obtained by reacting the amines with appropriate isocyanates.

30

Urethane residues can be prepared by preactivating the appropriate alcohols with carbonyldihydroxybenzotriazole ((HOBt)₂CO) and subsequently reacted with amines (Warass et al., *LIPS* 1998, 5, 125).

35

Alcohols can be obtained from carboxylic esters by reduction with LiAlH₄.

Aldehyde residues are obtained from alcohol precursors by oxidation for example under Swern conditions known

per se with DMSO/oxalyl chloride (Pansavath et al.,
Synthesis 1998, 436).

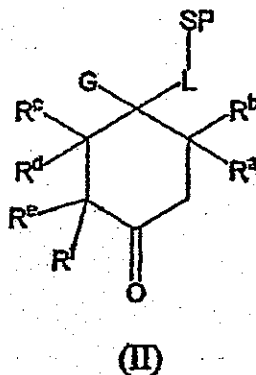
Substituted amine residues are obtained by reductive
5 amination of amines with aldehydes (*J. Org. Chem.* 1996,
61, 3489).

Ether residues can be obtained by deprotonating the
alcohol precursor with a base such as NaH under
10 Williams conditions known per se and subsequently
reacting with an alkyl halide.

Double bonds in the radicals can be introduced by
reacting an aldehyde or ketone precursor with
15 appropriate phosphonylides under Wittig conditions
known per se.

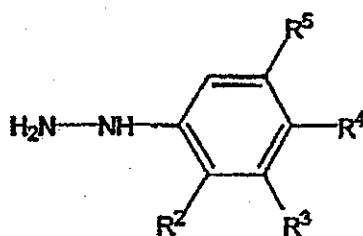
A solid-phase method for the preparation of compounds
of the invention of formula (I) preferably includes
20 steps (a) to (d) explained in detail below:

Step (a) proceeds essentially in analogy to a Fischer
indole synthesis, e.g. as described by Britten &
Lockwood, *J.C.S. Perkin I* 1974, 1824; Maki et al.,
25 *Chem. Pharm. Bull.* 1973, 21, 240 or Hutchins & Chapman,
Tetrahedron Lett. 1996, 37, 4869 and comprises the
condensation of a cyclohexanone derivative (II) which
contains the group G and is tethered to a solid
phase SP via a linker L suitable for forming the
30 radical R⁶



where, in the case where the radical R^7 is a hydrogen atom, a $C_1 - C_{12}$ alkyl, a $C_1 - C_{12}$ aralkyl or a hetaryl radical, the group G is equal to the radical R^7 , and in
5 the case where the radical R^7 has another one of the meanings indicated for R^7 in formula (I), the group G is equal to a group $-NH-Pg$, where Pg is a protective group, with a phenylhydrazine derivative (III) substituted by R^2 to R^5

10



(III)

in the presence of an acid, preferably acetic acid, and of a metal salt, preferably $ZnCl_2$. DMF is preferred as
15 solvent. The radicals R^a to R^f are defined as indicated above in formula (I). Certain substituents or groups may, where appropriate, also be present in protected form, in which case the protective groups are removed again by methods known per se at a suitable time during
20 the synthesis.

Particularly suitable solid phase SP for the purposes of the present invention are Rink amide-resins (Rink, *Tetrahedron Lett.* 1989, 28, 3787), HMB resins (Sheppard
25 et al., *Int. J. Peptide Protein Res.* 1982, 20, 451), Wang resins (Lu et al., *J. Org. Chem.* 1981, 46, 3433) or chlorotrityl-resins (Barlos et al., *Int. J. Peptide Protein Res.* 1991, 38, 562), where the cyclohexanone derivative (II) is to be tethered to the solid phase SP
30 by means of an (amino) carboxylic acid. Alcohol precursors of the cyclohexanone derivative (II) can be tethered by using the DHP linker (Liu & Elman, *J. Org.*

Chem. 1995, 60, 7712). Traceless tethering of aromatic precursors of the cyclohexanone derivative (II) to triazine resins is possible (Bräse et al., *Angew. Chem. Int. Ed.* 1998, 37, 3413).

5

The protective group Pg which is included where appropriate in the group G and protects an α -amino group $-NH_2$ is preferably a "Fmoc" (9-fluorenylmethoxycarbonyl) protective group, but may also be another customary amino protective group, e.g. from the series of the alkoxycarbonyl protective groups (such as, for example the "Z" (benzyloxycarbonyl) or the "Boc" (tert-butoxycarbonyl) group) or another suitable protective group, e.g. a "trityl" (triphenylmethyl) protective group.

15

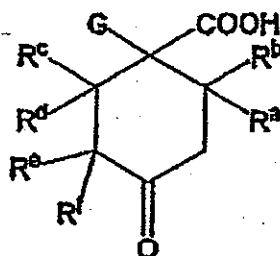
The constitution of the linker L is such that appropriate derivatization (steps (b) and (c)) and workup (step (d)) result in the desired radical R^6 with one of the meanings indicated above for R^6 in the final product, the tetrahydrocarbazole derivative of the general formula (I). To illustrate the constitution of the linker L, this may be explained below by way of example for the case where R^6 equals the group $-CONR^8R^9$.

25

In the case where the radical R^6 in the product of the invention of the formula (I) has the meaning $-CONR^8R^9$, firstly a compound $Pg-N(R^8)-R^{9'}-COOH$ forming the linker L is tethered by means of an activating reagent such as DCC (dicyclohexylcarbodiimide) or HATU (O-(7-azabenzotriazol-1-yl)-N,N'-N'-tetramethyluronium hexafluorophosphate) to the solid phase SP via free amino groups of the SP, where Pg and SP have the meaning indicated above, and $R^{9'}$ forms part of the later radical R^9 . The protective group Pg is subsequently eliminated, e.g. in the case of a Fmoc protective group by means of piperidine/DMF. This results in a compound $HR^8N-R^{9'}-CONH-SP$. The latter compound is then in turn reacted with a precursor of the cyclohexanone

35

derivative (II), namely the cyclohexanone carboxylic acid (II')



(II')

5

using an activating reagent such as DCC or HATU, finally resulting in the cyclohexanone derivative (II) as defined above. The meaning of the linker L in the case just described is -CONR⁸-R⁹'-CONH-SP. Any resulting
 10 isomers of whatever type (enantiomers, diastereomers or positional isomers) can be fractionated - as also elsewhere during the described preparation process - in a known manner by means of HPLC.

15 The actual step (a), i.e. the condensation of the cyclohexanone derivative (II) with the substituted phenylhydrazine derivative (III) and, where appropriate, elimination of the protective group Pg in the group G by means of, for example, piperidine (in
 20 the case of a Fmoc protective group) then takes place, so that a free α -amino group is produced again at this point.

In the case where the radical R⁷ is the group -NHCOR¹⁴,
 25 -NHSO₂R¹⁴, -NR¹²R¹³ (where R¹² and R¹³ are not both hydrogen atoms), -NHCONHR¹⁴ or -NHCOOR¹⁴, a derivatization of the now unprotected α -amino group of the resin-bound cyclohexanone derivative (II) finally takes place in step (b), so that the various
 30 alternative radicals R⁷ defined above can be performed.

Depending on the nature of the desired radical R^7 in the tetrahydrocarbozole final product (I) of the invention, the procedure for this is as follows:

- 5 In the case where R^7 is the group $-NHCOR^{14}$, the reaction product from step (a) is reacted with a carboxylic acid $R^{14}COOH$ in the presence of an activating reagent such as, for example, DCC or HATU and in the presence of a base such as, for example, DIPEA (diisopropyl-
- 10 ethylamine) or DMAP (4-dimethylaminopyridine) by known processes for forming peptide linkages (cf., for example, *Tetrahedron Lett.* 1994, 35, 2279; alternative (i)).
- 15 In the case where R^7 is a sulfonamide group $-NHSO_2R^{14}$, the reaction product from step (a) is reacted with a sulfonic acid derivative $R^{14}SO_2X$, where X is a leaving group, preferably a halogen atom, in particular a chlorine atom, in the presence of a base such as, for
- 20 example, DMAP or DIPEA (cf., for example, Gennari et al., *EJOC* 1998, 2437; alternative (ii)).

- In the case where R^7 is the group $-NR^{12}R^{13}$ (where R^{12} and R^{13} are not both hydrogen atoms), in the case where the
- 25 radical R^{12} is a hydrogen atom, the reaction product from step (a) is reacted with a reagent $R^{13}X$, where X is a leaving group such as, for example, a halide atom, in particular a chloride atom, in the presence of a base such as, for example, DBU or DIPEA (cf. Green, *JOC*
- 30 1995, 60, 4287 or *JOC* 1996, 61, 3849) or with an aldehyde $R^{13}CHO$ in the presence of a reducing agent such as, for example, $NaH/B(OAc)_3$. In the case where neither of the radicals R^{12} and R^{13} is a hydrogen atom, the reaction product from step (a) is reacted with a
- 35 ketone $R^{12}COR^{13}$ in the presence of a reducing agent (cf. Ellmann et al., *JOC* 1997, 62, 1240 or *Synth. Commun.* 1994, 609; alternative (iii)). In the case where both radicals R^{12} and R^{13} in R^7 equals $-NR^{12}R^{13}$ are hydrogen atoms, alternative (vi) below applies.

In the case where R^7 is the group $-NHCONHR^{14}$ (a urea derivative), the reaction product from step (a) is reacted with an isocyanate $R^{14}NCO$ (cf. Brown et al., JACS 1997, 119, 3288; alternative (iv)).

In the case where R^7 is a carbamate or urethane group $-NHCOOR^{14}$, the reaction product from step (a) is reacted with an alcohol HOR^{14} which has been preactivated by carbonyldihydroxybenzotriazole $((HOBt)_2CO)$ (cf. Warass et al., LIPS 1998, 5, 125; alternative (v)).

In the case where R^7 is a hydrogen atom, a C_1 - C_{12} alkyl, C_1 - C_{12} aralkyl, an aryl, a hetaryl radical or the group $-NH_2$ (i.e. both radicals R^{12} and R^{13} in R^7 equals $-NR^{12}R^{13}$ are hydrogen atoms), step (b) is omitted because no further derivatization is necessary (alternative (vi)).

Step (c), i.e. the derivatization on the indole nitrogen atom, also corresponds, in analogy to step (b) explained above, to various alternatives which are explained in detail below:

For cases (i) to (v) defined above in step (b), a deprotonation of the reaction product obtained in (b) takes place by means of a base such as, for example, NaH or NaHMDS and subsequent derivatization by means of a group R^1X , where X is a leaving group, e.g. a halide atom, in particular a chloride atom (cf. Collini & Ellingboe, Tetrahedron Lett. 1997, 38, 7963; Pecca & Albonico, J. Med. Chem. 1977, 20, 487 or Mooradian et al., J. Med. Chem. 1970, 13, 327).

For case (vi) defined above in step (b), i.e. when step (b) is omitted, in analogy to the above description a deprotonation of the reaction product obtained in (a) takes place by means of a base such as, for example NaH or NaHMDS and subsequent derivatization by means of a

group R^1X , where X is a leaving group, e.g. a halide atom, in particular a chloride atom.

Step (d) finally substantially includes the elimination
5 of the reaction product obtained in (c) from the solid phase SP. In the case of Wang, trityl, DHP and Rink amide resins, elimination of the reaction product obtained in (c) takes place with the aid of an acid, in particular with TFA (trifluoroacetic acid). In the case
10 of an aminolytic elimination from an HMB resin, the eliminating reagent used is, for example, ammonia in methanol. The desired product is then isolated in a conventional way.

15 Exemplary embodiments of the preparation of tetrahydrocarbazole derivatives of the invention are detailed below.

Examples

20

I. General synthetic methods for compounds of the invention

A *Coupling of carboxylic acids to the Rink amide-resin:*
25

0.1 mmol of Fmoc-protected Rink amide-resin (166 mg, loading 0.6 mmol/g) are preswollen with 1.5 ml of DMF in a vessel with bottom frit for 20 min. After aspiration, 1.5 ml of 20% piperidine/DMF are added and
30 stirred for 5 min. After aspiration, a further 1.5 ml of 20% piperidine/DMF are added and stirred for 15 min. Aspiration is followed by washing four times with DMF. Then 675 μ l of a 0.267 M solution of Fmoc-protected amino carboxylic acid in DMF, 675 μ l of HATU solution
35 (0.267 M in DMF) and 150 μ l of NMM solution (2.4 M in DMF) and 0.01 mmol of DMAP are added and stirred at 40°C for 4 h. After aspiration, the same reagents are again added and stirred at 40°C for 4 h. This is followed by aspiration and washing four times with DMF.

B Coupling of carboxylic acids to the trityl-resin:

2.98 mmol of Fmoc protected aminocarboxylic acid are dissolved in 30 ml of dry dichloromethane, mixed with 14.3 mmol (2.45 ml) of DIPEA and added to 2.98 mmol of 2-chlorotrityl chloride-resin (2 g, loading 1.49 mmol/g of resin). After shaking for two hours, the resin is filtered off with suction through a frit and washed three times with 20 ml of dichloromethane/MeOH/DIPEA 17:2:1. This is followed by washing three times with 20 ml of dichloromethane, three times with methanol and three times with 20 ml of ether and drying in vacuo. A resin with a loading of 0.5 to 1 mmol of amino carboxylic acid per g of resin is obtained.

C Coupling of carboxylic acids to the HMB-resin:

21.3 mmol of amino carboxylic acid and 21.3 mmol of HATU are dissolved in 60 ml of DMF and mixed with 63.9 mmol (10.9 ml) of DIPEA. After 5 minutes, 5 g of polystyrene-HMB-resin (loading 0.71 mmol/g of resin) are added and shaken at RT for 5 minutes. Then 21.3 mmol (2.6 g) of DMAP are added and shaken at RT for 1 h. The resin is subsequently filtered off with suction and washed once each with 100 ml of DMF, DCM and DMF. The resin is mixed with 100 ml of 10% Ac₂O (acetic anhydride)/DMF/5% DMAP and shaken for 15 min. Aspiration is followed by washing three times each with 100 ml of DCM and ether and drying in vacuo.

D Coupling of carboxylic acids to the Wang resin:

54.6 mmol of carboxylic acid and 27.3 mmol (4.2 ml) of DIC are dissolved in 500 ml of dry DCM, and stirred at RT for 10 min. After the precipitated urea has been filtered off, the solution is evaporated to dryness and the residue is dissolved in 160 ml of dry DMF. The solution is added to 4.55 mmol (5 g, loading 0.91 mmol/g of resin) of Wang resin preswollen in DMF, and 4.55 mmol (556 mg) of DMAP are added. After shaking at RT for 1.5 hours, the resin is filtered off with

suction and taken up in 100 ml of 10% Ac₂O/DMF/5% DMAP and shaken for 15 min. Aspiration is followed by washing three times each with 100 ml of DCM and ether and drying in vacuo.

5

E Coupling of an alcohol to the DHP-resin:

0.5 mmol of DHP-resin (0.5 g, loading density 1 mmol/g) are preswollen in 2 ml of dichloroethane for 15 min. To this are added 2 ml of a solution of 0.75 M alcohol/0.37 M pyridinium paratoluenesulfonate and stirred at 80°C for 16 h. Cooling to RT is followed by addition of 5 ml of pyridine, briefly shaking with inversion and filtration with suction. Washing is carried out twice each with 5 ml of DMF, DCM and
15 hexane.

F Deprotection of a resin-bound Fmoc protective group:

1.5 ml of 20% piperidine/DMF are added to 0.1 mmol of resin-bound Fmoc group and stirred for 5 min. After aspiration, 1.5 ml of 20% piperidine/DMF are again added and stirred for 15 min. Aspiration is followed by washing four times with DMF.

25 *G Coupling of a carboxylic acid to resin-bound amino functions:*

675 µl of a 0.267 M solution of Fmoc-protected amino carboxylic acid in DMF, 675 µl of HATU solution (0.267 M in DMF) and 150 µl of NMM solution (2.4 M in
30 DMF) and 0.01 mmol of DMAP are added to 0.1 mmol of resin-bound amino functions and stirred at 40°C for 4 h. After aspiration, the same reagents are added again and stirred at 40°C for 4 h. This is followed by aspiration and washing four times with DMF.

35

H Coupling of acetic acid to resin-bound amino functions:

1.5 ml of a solution of 10% acetic anhydride in DMF are added to 0.1 mmol of resin-bound amino functions and

stirred at RT for 15 min. This is followed by aspiration and washing four times with DMF.

I *Synthesis of tetrahydrocarbazoles starting from resin-bound cyclohexanones:*

Before the reaction, 0.1 mmol of cyclohexanone-resin are washed twice with 2 ml of DMF and twice with 2 ml of acetic acid. Then 1 ml of DMF and 2 ml of 0.5 M hydrazine/0.5 M ZnCl_2 in acetic acid are added to the resin and stirred at 70°C for 20 h. This is followed by aspiration and washing twice with 2 ml of acetic acid and 2 ml of DMF.

J *Synthesis of sulfonamides starting from resin-bound amides:*

The resin is washed twice with 2 ml each of DMF and DCE. 1 ml of 0.5 M sulfonyl chloride in DCE and 400 μl of 2.5 M NMM/1 eq. of 0.25 M DMAP in DMF are added to 0.1 mmol of resin-bound amine. Stirring at 60°C for 12 h is followed by aspiration and repetition of the coupling. Aspiration is followed by washing four times with 2000 ml of DMF.

K *Synthesis of ureas by reaction of resin-bound amine with isocyanates:*

2 ml of 0.5 M isocyanate in DCM are added to 0.1 mmol of resin-bound amine and stirred at RT for 18 h. Aspiration is followed by washing four times with DMF.

L *Synthesis of carbamates by reaction of resin-bound amine with preactivated alcohols:*

For the preactivation, 0.4 M alcohol and 0.39 M dibenzotriazolyl carbonate and 0.39 M pyridine are stirred in DMF at 40°C for 15 min. 1 mmol of resin-bound amine is mixed with 1 ml of preactivated alcohol, and 167 ml of 2.4 M NMM in DMF are added. Stirring at 60°C for 4 h is followed by aspiration and washing four times with DMF.

M Synthesis of N-alkylamines by N-alkylation of resin-bound amines with alkyl halides and catalytic KI:

1 ml of 0.5 M halide/0.05 M KI in DMF and 416 μ l of 2.4 M DIPEA in DMF are added to 0.1 mmol of resin-bound amine and stirred at 90°C for 12 h. After aspiration, the resin is washed four times with 2 ml of DMF.

N N-alkylation of resin-bound indole nitrogens with halide/NaH in DMF:

10 1 ml of DMF and 0.5 mmol of NaH (55% suspension in oil) are added to 0.1 mmol of resin-bound amine. After stirring at RT for 30 min, 1 ml of 0.5 M halide in DMF are added and stirred at 45°C for 8 h. This is followed by aspiration and washing twice each with 2 ml of methanol, DMF, methanol and DMF.

O Elimination from the Wang, trityl, DHP, Rink amide-resin:

20 2 ml of 95% TFA/5% H₂O solution are added to 0.1 mmol of resin and shaken at RT for 3 h. The resin is then filtered off and washed with a further 2 ml of TFA. The combined TFA solutions are evaporated to dryness and afford the crude products.

25 *P Aminolytic elimination from the HMB-resin:*

2 ml of DMF and 2 ml of 7 M NH₃ in methanol are added to 0.1 mmol of resin and shaken at RT for 18 h. The resin is then filtered off and washed with DMF. The combined solutions are evaporated to dryness and afford the crude product.

Preparation of required starting compounds:

35 3-[[[(9H-Fluoren-9-ylmethoxy)carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxylic acid 1

38.4 mmol (6.0 g) of 4,4-ethylenedioxycyclohexanone and 39.8 mmol (4.3 g) of phenylhydrazine are dissolved separately in 50 ml and 10 ml, respectively, of water,

and then mixed. The milky emulsion resulting after stirring for 10 min is extracted five times with ethyl acetate, dried with MgSO_4 and evaporated to dryness. Yield: 9.2 g of orange oil.

5

9.2 g of the unpurified phenylhydrazone are dissolved in 240 ml of toluene at RT, and 4.9 g of freshly ground ZnCl_2 are added. After refluxing with a water trap for 90 min, most of the toluene is distilled off, an excess of 2 N NaOH is added, and the mixture is extracted three times with ethyl acetate. The extract is washed with brine and dried with MgSO_4 , and the solvent is distilled off. The remaining black oil is purified on silica gel with ethyl acetate/hexane 1:9. Yield: 2.7 g of beige solid.

15

11.6 mmol (2.7 g) of 1,2,4,9-tetrahydrospiro[3H-carbazole-3,2'-[1,3]dioxolane] and 640 mg of p-toluenesulfonic acid are taken up in 70 ml of acetone and stirred at RT for 2.5 h. The solution is added to NaHCO_3 solution, extracted with ethyl acetate, washed with brine, dried with MgSO_4 and concentrated. 2.13 g of red-brown solid remain. Recrystallization from ether results in 1.1 g of beige-colored solid.

25

60.2 mmol (11.1 g) of 1,2,4,9-tetrahydrospiro-3H-carbazol-3-one, 8.3 g of KCN and 22.0 g of $(\text{NH}_4)_2\text{CO}_3$ are heated in 550 ml of 60% ethanol in an autoclave at 80°C for 3 h. After cooling to room temperature, the reaction mixture is added to ice-water, and the precipitated solid is filtered off. Yield: 10.1 g of gray solid.

30

44.2 mmol (11.3 g) of 1,2,4,9-tetrahydrospiro[3H-carbazole-3,4'-imidazolidine]-2',5'-dione is heated with 62 g of $\text{Ba}(\text{OH})_2 \times 8 \text{H}_2\text{O}$ in 145 ml of H_2O at 150°C for 13 h. After cooling to room temperature, the viscous mass is mixed with 37 g of $(\text{NH}_4)_2\text{CO}_3$ with stirring and heated at 100°C for 30 min. Cooling to

35

room temperature is followed by filtration, washing with water and evaporation of the filtrate to dryness. Yield: 7.7 g of beige solid.

- 5 26 mmol (5.8 g) of 3-amino-2,3,4,9-tetrahydro-1H-carbazole-3-carboxylic acid in 26 ml of 1 N NaOH and 26 mmol (8.76 g) of Fmoc-ONSu in 28 ml of acetonitrile are combined at room temperature and diluted with 130 ml of acetonitrile/H₂O 1:1. After two hours, the pH is readjusted to 9 with NEt₃ (1.5 ml) and the mixture is stirred at room temperature overnight. Then a further 6.3 g (18.7 mmol) of Fmoc-ONSu dissolved in 19 ml of acetonitrile are added, and stirring is continued for two hours while controlling the pH. Removal of the acetonitrile by distillation is followed by acidification with 0.01 M HCl and extraction with ethyl acetate. The extract is washed until neutral, dried with Na₂SO₄ and evaporated to dryness in a rotary evaporator. Recrystallization takes place from ether/hexane. Yield: 10.7 g.

¹H NMR (d⁶ DMSO): δ = 2.07 ppm (m, 1H); 2.50 (m, 1H); 2.70 (bs, 2H); 3.04 (q, 2H); 4.17 (m, 2H); 4.28 (m, 2H); 6.92 (tr, 2H); 6.99 (tr, 2H); 7.23 (tr, 2H); 7.24-7.35 (m, 3H); 7.38 (tr, 2H); 7.62 (s, 1H); 7.68 (dd, 2H); 7.87 (d, 2H); 10.71 (s, 1H).

Melting point: 119°C

Fractionation into the two enantiomers takes place by chiral HPLC.

(R)-3-[[(9H-Fluoren-9-ylmethoxy)carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxylic acid 1a

t_R = 6.4 min (Chiralcel OD 10 μ m LC50 250 $\times$ 4.6 cm, hexane/isopropanol 75:25, 80 ml/min)

(S)-3-[[(9H-Fluoren-9-ylmethoxy)carbonyl]amino]-

2,3,4,9-tetrahydro-1H-carbazole-3-carboxylic acid 1b

t_R = 7.5 min (Chiralcel OD 10 μ m LC50 250 $\times$ 4.6 cm, hexane/isopropanol 75:25, 80 ml/min)

1-[[*(9H-Fluoren-9-ylmethoxy) carbonyl*]-amino]-4-oxocyclohexanecarboxylic acid 2

320 mmol (50 g) of 4,4-ethylenedioxcyclohexanone are
5 suspended in 800 ml of 50% EtOH, and 1500 mmol
(144.5 g) of $(\text{NH}_4)_2\text{CO}_3$ and 640 mmol (41.7 g) of KCN are
added. After stirring at 60°C for 5 h, the ethanol is
removed in vacuo, and the aqueous residue after cooling
with ice is filtered off, washed with water and dried.
10 Yield: 72.4 g of 4,4-1,4-dioxo-9,11-diazadi-
spiro[4.2.4.2]tetradecane-10,12-dione.

295 mmol (66.8 g) of 4,4-1,4-dioxo-9,11-diazadi-
spiro[4.2.4.2]tetradecane-10,12-dione and 826 mmol
15 (260.6 g) of $\text{Ba}(\text{OH})_2 \times 8 \text{H}_2\text{O}$ are stirred in 2.5 l at
150°C in an autoclave for 6 h. After cooling to room
temperature, 1032 mmol (99.2 g) of $(\text{NH}_4)_2\text{CO}_3$ are added to
the solution and stirred at 60°C for 1 h. The
suspension is filtered and washed, and the filtrate is
20 lyophilized. The residue is recrystallized from
 $\text{H}_2\text{O}/\text{MeOH}$. Yield: 45.4 g of 8-amino-1,4-dioxo-
spiro[4,5]decane-8-carboxylic acid.

213 mmol (42.9 g) of 8-amino-1,4-dioxaspiro[4,5]decane-
25 8-carboxylic acid in 213 ml of 1 N NaOH and 213 mmol
(71.9 g) of Fmoc-ONSu in 240 ml of acetonitrile are
combined and diluted with 1000 ml of acetonitrile/ H_2O
1:1. Adjustment of the pH to 9 is followed by stirring
at room temperature overnight. Removal of the
30 acetonitrile in a rotary evaporator is followed by
acidification with 0.01 M HCl and extraction with ethyl
acetate. The extract is washed until neutral, dried
with Na_2SO_4 and evaporated to dryness. The residue is
recrystallized from ethyl acetate/hexane. Yield: 79.0 g
35 of 8-[[*(9H-fluoren-9-ylmethoxy) carbonyl*]-amino]-1,4-
dioxaspiro[4,5]decane-8-carboxylic acid.

187 mmol (79 g) of 8-[[*(9H-fluoren-9-ylmethoxy)-*
carbonyl]-amino]-1,4-dioxaspiro[4,5]decane-8-carboxylic

acid are taken up in 3.5 l of acetone/0.1 M HCl 1:1 and stirred at room temperature for 4 h. The acetone is stripped off in a rotary evaporator, and the precipitated product is filtered off, washed with water and dried. Yield: 68.7 g of 2.

^1H NMR (d^6 DMSO): δ = 1.52-1.73 (m, 4H); 1.82-2.14 (m, 4H); 4.27 (m, 3H); 7.85 (tr, 2H); 7.42 (tr, 2H); 7.67 (s, 1H); 7.75 (d, 2H); 7.91 (d, 2H).

Melting point: 157°C

4-Oxocyclohexanecarboxylic acid 3

20 mmol (3.4 g) of ethyl 4-oxocyclohexanecarboxylate are suspended in 40 ml of 2% H_2SO_4 and stirred at 90°C for 2 h. This is followed by extraction four times with ethyl acetate, drying with Na_2SO_4 and removal of the solvent. Recrystallization from ether/hexane affords 2.9 g of white solid 3.

^1H NMR (d^6 DMSO): δ = 1.72 (m, 2H); 2.08-2.18 (m, 2H); 2.19-2.47 (m, 4H); 2.72 (m, 1H); 12.23 (bs, 1H).

4-Chloro-3-[[(phenylamino) carbonyl] amino]benzeneacetic acid 4

18.55 mmol (2.21 g) of SOCl_2 are slowly added to 18.55 mmol (4 g) of 4-chloro-3-nitrobenzeneacetic acid in 50 ml of MeOH while cooling in ice and stirring. After stirring for 30 min, the mixture is allowed to warm to RT and a further 3.71 mmol (0.44 g) of SOCl_2 are added. Stirring overnight is followed by heating to reflux for 30 min. Stripping off the solvent is followed by recrystallization from ether/hexane. Yield: 3.43 g of methyl 4-chloro-3-nitrobenzeneacetate as yellowish solid.

13.07 mmol (3.0 g) of methyl 4-chloro-3-nitrobenzeneacetate and 198.8 mmol (13.0 g) of Zn dust are heated to reflux in 500 ml of MeOH for 10 min. Then, under reflux, 13 ml of conc. HCl are added

dropwise, and refluxing is continued for 30 min. The suspension is filtered hot, the methanol is distilled off, and the residue is adjusted to pH 14 with a NaHCO_3 solution. Extraction with ethyl acetate, drying with Na_2SO_4 and removal of the solvent by distillation affords 2.3 g of methyl 3-amino-4-chlorobenzeneacetate as beige solid.

2.08 mmol (415 mg) of methyl 3-amino-4-chlorobenzeneacetate are dissolved in 40 ml of DCM and, at 0°C , 0.83 mmol (246.3 mg) of triphosgene and 0.6 ml of pyridine are added. After stirring at 0°C for one hour, 10.4 mmol (1.11 g) of benzylamine are added, and stirring is continued at room temperature overnight. Extraction is carried out with $\text{DCM}/\text{H}_2\text{O}$, the organic phase is dried, and the solvent is removed. Yield: 727 mg of methyl 4-chloro-3-[[(phenylamino)-carbonyl]amino]benzeneacetate.

2.98 mmol (990 mg) of methyl 4-chloro-3-[[(phenylamino)carbonyl]amino]benzeneacetate are taken up in 10 ml of methanol, and 6 mmol of 1 N NaOH are added. After stirring at RT for 2 h, the methanol is distilled off and the residue is acidified to pH 2-3 with 1 M HCl . Extraction is carried out with ethyl acetate, and drying with Na_2SO_4 , and the solvent is removed. Recrystallization takes place from boiling isopropanol. Yield: 830 mg of white solid 4.

^1H NMR (d^6 DMSO): δ = 3.57 (s, 2H); 6.92 (d, 1H); 6.99 (tr, 1H); 7.35-7.50 (m, 3H); 8.10 (s, 1H); 8.30 (s, 1H); 9.42 (s, 1H); 12.40 (bs, 1H).

4-Chloro-3-[[[(phenylmethyl)amino]carbonyl]amino]-benzeneacetic acid 5

2.08 mmol (415 mg) of methyl 3-amino-4-chlorobenzeneacetate are mixed with 10.4 mmol (969 mg) of aniline as described under 4.) and worked up analogously. Yield: 662 mg of solid.

For the ester cleavage, 2.47 mmol (790 mg) of methyl 4-chloro-3-

[[[(phenylmethyl)amino]carbonyl]amino]benzeneacetate

- 5 are hydrolyzed with 1 N NaOH in analogy to the above method. The product 5 is obtained without recrystallization. Yield: 693 mg of yellowish solid.

ES-MS: 319 (M+H⁺)

- 10 4-Chloro-3-[[[(4-pyridinylamino)carbonyl]amino]benzeneacetic acid 6

2.08 mmol (415 mg) of methyl 3-amino-4-chlorobenzeneacetate are mixed with 10.4 mmol (979 mg) of 4-aminopyridine as described under 4.) and worked up
15 analogously. Yield: 664 mg of solid.

For the ester cleavage, 2.63 mmol (840 mg) of methyl 4-chloro-3-[[[(4-pyridinylamino)carbonyl]amino]

- 20 benzeneacetate are hydrolyzed with 1 N NaOH in analogy to the above method. The product 6 is obtained without recrystallization. Yield: 481 mg of yellowish solid.

- ¹H NMR (d⁶ DMSO): δ = 3.57 (s, 2H); 6.94 (d, 1H); 7.40 (m, 3H); 8.05 (s, 1H); 8.35 (d, 2H); 8.50 (s, 1H); 9.92
25 (s, 1H); 12.40 (bs, 1H)

4-Chloro-3-[[[(2-pyridinylamino)carbonyl]amino]benzeneacetic acid 7

- 2.08 mmol (415 mg) of methyl 3-amino-4-chlorobenzeneacetate are mixed with 10.4 mmol (979 mg) of 2-aminopyridine as described under 4.) and worked up
30 analogously. Yield: 617 mg of solid.

- 35 For the ester cleavage, 2.47 mmol (790 mg) of methyl 4-chloro-3-[[[(2-

pyridinylamino)carbonyl]amino]benzeneacetate are hydrolyzed with 1 N NaOH in analogy to the above method. The product 7 is obtained without recrystallization. Yield: 693 mg of yellowish solid.

¹H NMR (d⁶ DMSO): δ = 3.59 (s, 2H); 6.94 (dd, 1H); 7.03 (dd, 1H); 7.22 (d, 1H); 7.42 (d, 1H); 7.78 (dtr, 1H); 8.29 (m, 2H); 10.02 (s, 1H); 11.82 (bs, 1H); 12.50 (s, 1H).

II. Examples of compounds (I) of the invention

Example 1:

0.3 mmol (42.6 mg) of 4-oxocyclohexanecarboxylic acid are dissolved in 1 ml of acetic acid and added to a suspension of 0.3 mmol (43.3 g) of phenylhydrazine hydrochloride and 0.3 mmol (40.0 mg) of ZnCl₂ in 1 ml of acetic acid. Stirring at 70°C for 20 h is followed by dilution with 20 ml of water and extraction with ethyl acetate. The ethyl acetate phase is washed with water, dried over Na₂SO₄ and evaporated to dryness. Yield: 65.6 mg (100%) of white solid.

Name	Number	M _{find}	M _{calc}
2,3,4,9-Tetrahydro-1H-carbazole-3-carboxylic acid	<u>8</u>	215	215.2507

The column headings (name, number of the compound, M_{find} (measured molecular mass), M_{calc} (calculated molecular mass)) which are introduced here also apply to the following examples and are therefore not repeated again.

Example 2:

Synthesis takes place on the 0.2 mmol scale by methods A, I and O.

2,3,4,9-Tetrahydro-1H-carbazole-3-carboxamide	<u>9</u>	214	214.2666
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Example 3:

Synthesis takes place on the 0.2 mmol scale by methods A, F, G, I and O.

5	<i>N</i> -[(1 <i>S</i>)-1-(Aminocarbonyl)-2-methylpropyl]-(3 <i>S</i>)-2,3,4,9-tetrahydro-1 <i>H</i> -carbazole-3-carboxamide	<u>10a</u>	314	313.3987
10	<i>N</i> -[(1 <i>S</i>)-1-(Aminocarbonyl)-2-methylpropyl]-(3 <i>R</i>)-2,3,4,9-tetrahydro-1 <i>H</i> -carbazole-3-carboxamide	<u>10b</u>	314	313.3987
15	<i>N</i> -(2-Amino-2-oxoethyl)-2,3,4,9-tetrahydro-1 <i>H</i> -carbazole-3-carboxamide	<u>11</u>	271	271.3183

Example 4:

Synthesis takes place on the 0.2 mmol scale by methods D, F, G, F, G, I and O.

20	<i>N</i> -[(3 <i>S</i>)-(2,3,4,9-Tetrahydro-1 <i>H</i> -carbazol-3-yl)carbonyl]-L-valyl-L-glutamine	<u>12a</u>	442	442.513
25	<i>N</i> -[(3 <i>R</i>)-(2,3,4,9-Tetrahydro-1 <i>H</i> -carbazol-3-yl)carbonyl]-L-valyl-L-glutamine, Isomer B	<u>12b</u>	442	442.513

Example 5:

30 Synthesis takes place on the 0.2 mmol scale by methods D, F, G, I, F and O:

35	<i>N</i> -[(3 <i>S</i>)-3-Amino-2,3,4,9-tetrahydro-1 <i>H</i> -carbazol-3-yl)carbonyl]-L-alanine	<u>13</u>	301	301.3441
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Example 6:

0.1 mmol of carboxylic acid, 0.1 mmol of HOBt and 0.15 mmol of amine component are dissolved in 15 ml of

dry DMF (also THF, DCM), and, while cooling in ice and stirring, 0.5 mmol of NMM is added. After about 15 min, 0.15 mmol of EDCI x HCl is added, and the mixture is stirred for one hour, warmed to room temperature and stirred overnight. For workup, the solvent is stripped off, and the product is dissolved in ethyl acetate and washed twice each with 0.1 N HCl and saturated NaCl solution. Drying and stripping off the solvent are followed if necessary by recrystallization.

10

9H-Fluoren-9-ylmethyl[(3S)-3-[[[(4-bromophenyl)methyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbamate

14 620 620.5439

15

Methyl N-[[[(3S)-3-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-alaninate

15 537 537.6129

20

Example 7:

Synthesis takes place on the 0.2 mmol scale by methods A, F, G, F, G, F, G and O.

<i>N</i> -[[<i>(3R)</i> -3-[[<i>(2S,3S)</i> -2-[[<i>(9H</i> -Fluoren-9-ylmethoxy)carbonyl]amino]-3-methyl-1-oxopentyl]amino]-2,3,4,9-tetrahydro-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>16</u>	779	777.9178
<i>N</i> -[[<i>(3S)</i> -3-[[<i>(2S,3S)</i> -2-[[<i>(9H</i> -Fluoren-9-ylmethoxy)carbonyl]amino]-3-methyl-1-oxopentyl]amino]-2,3,4,9-tetrahydro-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>17</u>	779	777.9178
<i>N</i> -[[<i>(3R)</i> -2,3,4,9-Tetrahydro-3-[(1-oxo-2,3-diphenylpropyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>18</u>	651	650.7758
<i>N</i> -[[<i>(3S)</i> -2,3,4,9-Tetrahydro-3-[(1-oxo-2,3-diphenylpropyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide, Isomer A	<u>19</u>	651	650.7758
<i>N</i> -[[<i>(3S)</i> -2,3,4,9-Tetrahydro-3-[(1-oxo-2,3-diphenylpropyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide, Isomer B	<u>20</u>	651	650.7758
<i>N</i> -[[<i>(3S)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S,3S)</i> -3-methyl-1-oxo-2-[(1-oxo-3-phenylpropyl)amino]pentyl]amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>21</u>	688	687.8371

<i>N</i> -[[<i>(3R)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S,3S)</i> -3-methyl-1-oxo-2- [(1-oxo-3-phenylpropyl)amino]pentyl]amino]-1 <i>H</i> -carbazol- 3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>22</u>	688	687.8371
<i>N</i> -[[<i>(3S)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S)</i> -1-oxo-2- [(phenylmethoxy)carbonyl]amino]propyl]amino]-1 <i>H</i> - carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>23</u>	648	647.7289
<i>N</i> -[[<i>(3R)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S)</i> -1-oxo-2- [(phenylmethoxy)carbonyl]amino]propyl]amino]-1 <i>H</i> - carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>24</u>	648	647.7289
<i>N</i> -[[<i>(3R)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S,3S)</i> -3-methyl-1-oxo- 2-[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1 <i>H</i> - carbazol-3-yl]carbonyl]- <i>L</i> -alanyl- <i>L</i> -aspartamide	<u>25</u>	662	661.7557
<i>N</i> -[[<i>(3R)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S,3S)</i> -3-methyl-1-oxo- 2-[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1 <i>H</i> - carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -alaninamide	<u>26</u>	647	646.7844
<i>N</i> -[[<i>(3S)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S,3S)</i> -3-methyl-1-oxo-2- [(phenylmethoxy)carbonyl]amino]pentyl]amino]-1 <i>H</i> - carbazol-3-yl]carbonyl]- <i>D</i> -valyl- <i>L</i> -aspartamide	<u>27</u>	690	689.8093
<i>N</i> -[[<i>(3R)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S,3S)</i> -3-methyl-1-oxo- 2-[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1 <i>H</i> - carbazol-3-yl]carbonyl]- <i>D</i> -valyl- <i>L</i> -aspartamide	<u>28</u>	690	689.8093
<i>N</i> -[[<i>(3R)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S,3S)</i> -3-methyl-1-oxo- 2-[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1 <i>H</i> - carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>D</i> -aspartamide	<u>29</u>	690	689.8093
<i>N</i> -[[<i>(3S)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S,3S)</i> -3-methyl-1-oxo-2- [(phenylmethoxy)carbonyl]amino]pentyl]amino]-1 <i>H</i> - carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>D</i> -aspartamide	<u>30</u>	690	689.8093
<i>N</i> -[[<i>(3S)</i> -2,3,4,9-Tetrahydro-3-[[<i>(2S,3S)</i> -3-methyl-1-oxo-2- [(phenylmethoxy)carbonyl]amino]pentyl]amino]-1 <i>H</i> - carbazol-3-yl]carbonyl]- <i>L</i> -alanyl- <i>L</i> -aspartamide	<u>31</u>	662	661.7557
<i>N</i> -[[<i>(3S)</i> -2,3,4,9-Tetrahydro-3-[(phenylacetyl)amino]-1 <i>H</i> - carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>32</u>	651	560.6514
<i>N</i> -[[<i>(3R)</i> -2,3,4,9-Tetrahydro-3-[(1-oxo-3- phenylpropyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>33</u>	576	574.6782
<i>N</i> -[[<i>(3S)</i> -2,3,4,9-Tetrahydro-3-[(1-oxo-3- phenylpropyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>34</u>	575	574.6782

<i>N</i> -[[[(3 <i>S</i>)-2,3,4,9-Tetrahydro-3-[[[(2 <i>S</i> ,3 <i>S</i>)-3-methyl-1-oxo-2-[[[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -alaninamide	<u>35</u>	647	646.7844
<i>N</i> -[[[(3 <i>R</i>)-2,3,4,9-Tetrahydro-3-[(phenylacetyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>36</u>	561	560.6514
<i>N</i> -[[[(3 <i>R</i>)-2,3,4,9-Tetrahydro-3-[(1-oxo-4-phenylbutyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>37</u>	589	588.705
<i>N</i> -[[[(3 <i>S</i>)-2,3,4,9-Tetrahydro-3-[(1-oxo-4-phenylbutyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>38</u>	589	588.705
<i>N</i> -[[[(3 <i>R</i>)-3-[(Diphenylacetyl)amino]-2,3,4,9-tetrahydro-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>39</u>	637	636.749
<i>N</i> -[[[(3 <i>S</i>)-3-[(Diphenylacetyl)amino]-2,3,4,9-tetrahydro-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide	<u>40</u>	637	636.749
<i>N</i> -[[[(3 <i>R</i>)-2,3,4,9-Tetrahydro-3-[(1-oxo-2-phenylpropyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide, Isomer A	<u>41</u>	575	574.6782
<i>N</i> -[[[(3 <i>R</i>)-2,3,4,9-Tetrahydro-3-[(3-methyl-1-oxo-2-phenylpentyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide, Isomer B	<u>42</u>	617	616.7586
<i>N</i> -[[[(3 <i>S</i>)-2,3,4,9-Tetrahydro-3-[(3-methyl-1-oxo-2-phenylpentyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide, Isomer A	<u>43</u>	617	616.7586
<i>N</i> -[[[(3 <i>S</i>)-2,3,4,9-Tetrahydro-3-[(3-methyl-1-oxo-2-phenylpentyl)amino]-1 <i>H</i> -carbazol-3-yl]carbonyl]- <i>L</i> -valyl- <i>L</i> -aspartamide, Isomer B	<u>44</u>	617	616.7586
Phenylmethyl [(1 <i>S</i> ,2 <i>S</i>)-1-[[[(3 <i>R</i>)-3-[[[(1 <i>S</i>)-1-[[[4-(aminocarbonyl)phenyl]amino]carbonyl]-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1 <i>H</i> -carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>45</u>	695	694.8284
Phenylmethyl [(1 <i>S</i> ,2 <i>S</i>)-1-[[[(3 <i>S</i>)-3-[[[(1 <i>S</i>)-1-[[[4-(aminocarbonyl)phenyl]amino]carbonyl]-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1 <i>H</i> -carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>46</u>	695	694.8284

N-[[[(3S)-2,3,4,9-Tetrahydro-3-[(3-methyl-1-oxo-2-phenylbutyl)amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide, Isomer A	<u>47</u>	603	602.7318
N-[[[(3S)-2,3,4,9-Tetrahydro-3-[(3-methyl-1-oxo-2-phenylbutyl)amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide, Isomer B	<u>48</u>	603	602.7318
N-[[[(3R)-2,3,4,9-Tetrahydro-3-[(3-methyl-1-oxo-2-phenylbutyl)amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>49</u>	603	602.7318
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-[[[4-(aminocarbonyl)cyclohexyl]methyl]amino]carbonyl]-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>50</u>	715	714.9026
N-[[[(3R)-2,3,4,9-Tetrahydro-3-[(3-phenoxyphenyl)acetyl]amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>51</u>	653	652.748
N-[[[(3S)-2,3,4,9-Tetrahydro-3-[(3-phenoxyphenyl)acetyl]amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>52</u>	653	652.748
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-[[[3-(aminocarbonyl)phenyl]methyl]amino]carbonyl]-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>53</u>	709	708.8552
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-[[[3-(aminocarbonyl)phenyl]methyl]amino]carbonyl]-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>54</u>	709	708.8552
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(2R)-1-oxo-2-[(1-oxo-3-phenylpropyl)amino]-3-phenylpropyl]amino]-1H-carbazole-3-carboxamide	<u>55</u>	608	607.7509
N-[[[(3S)-2,3,4,9-Tetrahydro-3-[(1-oxo-2-phenylpropyl)amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>56</u>	575	574.6782
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-[[[4-(aminocarbonyl)cyclohexyl]methyl]amino]carbonyl]-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>57</u>	715	714.9026

Example 8:

Synthesis takes place on the 0.2 mmol scale by methods A, F, G, F, G and O.

Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>58</u>	576	575.7059
N-[[[(3S)-3-[[[(9H-Fluoren-9-ylmethoxy)carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>59</u>	665	664.759
N-[[[(3R)-3-[[[(9H-Fluoren-9-ylmethoxy)carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>60</u>	665	664.759
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>61</u>	576	575.7059
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[4-(aminocarbonyl)phenyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>62</u>	596	595.6963
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[4-(aminocarbonyl)phenyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>63</u>	596	595.6963
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>64</u>	590	589.7327
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>65</u>	590	589.7327
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>66</u>	623	623.7499

Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>67</u>	623	623.7499
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1-oxo-2-phenylpropyl)amino]-1H-carbazole-3-carboxamide	<u>68</u>	460	460.5748
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[3-(aminocarbonyl)phenyl]methyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>69</u>	610	609.7231
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[3-(aminocarbonyl)phenyl]methyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>70</u>	610	609.7231
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[4-(aminocarbonyl)cyclohexyl]methyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>71</u>	615	615.7705
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[4-(aminocarbonyl)cyclohexyl]methyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>72</u>	615	615.7705
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[3-(aminocarbonyl)phenyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>73</u>	596	595.6963
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[3-(aminocarbonyl)phenyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>74</u>	596	595.6963
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>75</u>	610	609.7231
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1R)-2-amino-2-oxo-1-phenylethyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>76</u>	610	609.7231
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(2-amino-2-oxo-1-phenylethyl)amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate,	<u>77</u>	609	609.7231

Isomer A

Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[(2-amino-2-oxo-1-phenylethyl)amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, Isomer B	<u>78</u>	609	609.7231
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(3-hydroxyphenyl)acetyl]amino]-1H-carbazole-3-carboxamide	<u>79</u>	462	462.547
(3R)-3-[[[3-(Acetyloxy)phenyl]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>80</u>	504	504.5838
3-[2-[(3R)-3-[[[(1S)-1-(Aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]-2-oxoethyl]phenyl 3-hydroxybenzenacetate	<u>81</u>	597	596.8804
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(hydroxyphenylacetyl)amino]-1H-carbazole-3-carboxamide	<u>82</u>	462	462.547
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-bromophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>83</u>	525	525.4441
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[2-chlorophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>84</u>	481	480.9931
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[3-chlor-4-hydroxyphenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>85</u>	497	496.9921
(3R)-3-[[[4-(Acetyloxy)-3-chlorophenyl]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>86</u>	539	539.0289
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[3-fluor-4-hydroxyphenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>87</u>	481	480.5371

(3R)-3-[[[4-(Acetyloxy)-3-fluorophenyl]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>88</u>	523	522.5739
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[4-nitrophenyl]acetyl]amino]-1H-carbazol-3-carboxamide	<u>89</u>	492	491.5451
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[2,4-dichlorophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>90</u>	515	515.4362
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-fluorophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>91</u>	464	464.5381
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[4-hydroxyphenyl]acetyl]amino]-1H-carbazol-3-carboxamide	<u>92</u>	462	462.547
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[2-bromophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>93</u>	526	525.4441
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[2-nitrophenyl]acetyl]amino]-1H-carbazol-3-carboxamide	<u>94</u>	491	491.5451
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[3-nitrophenyl]acetyl]amino]-1H-carbazol-3-carboxamide	<u>95</u>	491	491.5451
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[3-bromophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>96</u>	525	525.4441
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[2-chloro-4-fluorophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>97</u>	499	498.9832
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[1,1'-biphenyl]-4-ylacetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>98</u>	523	522.6458
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[3,5-dimethylphenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>99</u>	475	474.8016

(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[(1,3-benzodioxol-5-ylacetyl)amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>100</u>	480	490.557
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[(3-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>101</u>	481	480.9931
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(3-methylphenyl)acetyl]amino]-1H-carbazol-3-carboxamide	<u>102</u>	461	460.5748
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[(2-fluorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>103</u>	464	464.5381
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(2-methylphenyl)acetyl]amino]-1H-carbazol-3-carboxamide	<u>104</u>	461	460.5748
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[4-(1-methylethyl)phenyl]acetyl]amino]-1H-carbazol-3-carboxamide	<u>105</u>	489	488.6284
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[4-(dimethylamino)phenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>106</u>	490	489.6165
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[4-(methylsulfonyl)phenyl]acetyl]amino]-1H-carbazol-3-carboxamide	<u>107</u>	524	524.6388
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[(3-fluor-4-methylphenyl)acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide	<u>108</u>	478	478.5649

Example 9:

Synthesis takes place on the 0.2 mmol scale by methods B, F, G, F, G, F, G and O.

5

N-[(3R)-2,3,4,9-Tetrahydro-3-[(2S,3S)-3-methyl-1-oxo-2-[[[phenyl(methoxy)carbonyl]amino]pentyl]amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-asparagine	<u>109</u>	691	690.7934
N-[(3S)-2,3,4,9-Tetrahydro-3-[(2S,3S)-3-methyl-1-oxo-2-[[[phenyl(methoxy)carbonyl]amino]pentyl]amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-asparagine	<u>110</u>	691	690.7934

Example 10:

Synthesis takes place on the 0.2 mmol scale by methods A, F, G, F, G, F, G, F, H and O.

N-[[<u>(3R)</u>]-3-[[<u>(2S,3S)</u>]-2-(Acetylamino)-3-methyl-1-oxopentyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>111</u>	598	597.7127
N-[[<u>(3S)</u>]-3-[[<u>(2S,3S)</u>]-2-(Acetylamino)-3-methyl-1-oxopentyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>112</u>	598	597.7127
N-[[<u>(3R)</u>]-3-[[<u>(2R,3R)</u>]-2-(Acetylamino)-3-methyl-1-oxopentyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>113</u>	598	597.7127
N-[[<u>(3S)</u>]-3-[[<u>(2R,3R)</u>]-2-(Acetylamino)-3-methyl-1-oxopentyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>114</u>	598	597.7127

5

Example 11:

Synthesis takes place on the 0.2 mmol scale by methods A, F, G, F, G, F, H and O.

10

N-[[<u>(3R)</u>]-3-(Acetylamino)-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>115</u>	484	484.5538
N-[[<u>(3S)</u>]-3-(Acetylamino)-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>116</u>	484	484.5538
N-[[<u>(3S)</u>]-3-(Acetylamino)-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-D-valyl-L-aspartamide	<u>117</u>	484	484.5538
N-[[<u>(3S)</u>]-3-(Acetylamino)-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-D-aspartamide	<u>118</u>	484	484.5538

Example 12:

15 Synthesis takes place on the 0.2 mmol scale by methods A, F, G and O.

Phenylmethyl [(1S,2S)-1-[[[(3R)-3-(aminocarbonyl)-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate 119 476 476.5738

Phenylmethyl [(1S,2S)-1-[[[(3S)-3-(aminocarbonyl)-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate 120 476 476.5738

Example 13:

Synthesis takes place on the 0.2 mmol scale by methods

5 A, F, G, F, G, F, G, F, G and O.

N-[[[(3R)-2,3,4,9-Tetrahydro-3-[[[(2S)-1-oxo-2-[(1-oxo-3-phenylpropyl)amino]-3-phenylpropyl]amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide] 121 722 721.8543

N-[[[(3R)-2,3,4,9-Tetrahydro-3-[[[(2R,3R)-3-methyl-1-oxo-2-[(1-oxo-3-phenylpropyl)amino]pentyl]amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide] 122 688 687.8371

Example 14:

10

Synthesis takes place on the 0.2 mmol scale by methods

D, F, G, F, G and O.

N-[[[(3R)-2,3,4,9-Tetrahydro-3-[[[(2S,3S)-3-methyl-1-oxo-2-[[[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1H-carbazol-3-yl]carbonyl]-L-valine, N-[[[(3R)-2,3,4,9-Tetrahydro-3-[[[(2S)-3-methyl-1-oxo-2-[[[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1H-carbazol-3-yl]carbonyl]-L-valine] 123 577 576.69

N-[[[(3S)-2,3,4,9-Tetrahydro-3-[[[(2S,3S)-3-methyl-1-oxo-2-[[[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1H-carbazol-3-yl]carbonyl]-L-valine] 124 577 576.69

15

Example 15:

Synthesis takes place on the 0.2 mmol scale by methods

C, F, G, F, G, F, G and P

N-[[[(3R)-3-[[[(2S,3S)-2-[[[(1S)-Dimethylethoxy)carbonyl]amino]-3-methyl-1-oxopentyl]amino]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide

	<u>125</u>	656	655.7921
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Example 16:

Synthesis takes place on the 0.2 mmol scale by methods

5 A, F, G, F, G, F and O.

N-[(3S)-3-Amino-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide

	<u>126</u>	442	442.517
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N-[[[(3R)-3-Amino-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide

	<u>127</u>	442	442.517
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(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(2S,3S)-2-amino-3-methyl-1-oxopentyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide

	<u>128</u>	441	441.5725
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Example 17:

10 Synthesis takes place on the 0.2 mmol scale by methods

D, F, G, F, G, F, H and O.

N-[(3S)-3-(Acetylamino)-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbonyl]-L-valyl-L-asparagine

	<u>129</u>	485	485.5379
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15 *Example 18:*

Synthesis takes place on the 0.2 mmol scale by methods

A, F, G, F, H and O.

(3R)-3-(Acetylamino)-N-[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide

	<u>130</u>	418	418.4944
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(3S)-3-(Acetylamino)-N-[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-2,3,4,9-tetrahydro-1H-carbazol-3-carboxamide

	<u>131</u>	418	418.4944
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Example 19:

Synthesis takes place on the 0.2 mmol scale by methods B, F, G and O.

(3S)-2,3,4,9-Tetrahydro-3-[[[(2S,3S)-3-methyl-1-oxo-2- [[[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1H- carbazole-3-carboxylic acid	<u>132</u>	478	477,5579
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Example 20:

Synthesis takes place on the 0.2 mmol scale by methods B, F, G, F and O.

(3S)-3-[[[(2,2-Diphenylethyl)amino]acetyl]amino]-2,3,4,9- tetrahydro-1H-carbazole-3-carboxylic acid	<u>134</u>	468	467,5681
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Example 21:

Synthesis takes place on the 0.2 mmol scale by methods A, F, G, F, H and O.

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(3S)-3-(Acetylamino)-N-[[3- (aminocarbonyl)phenyl]methyl]-2,3,4,9-tetrahydro-1H- carbazole-3-carboxamide	<u>135</u>	404	404,4678
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(3S)-3-(Acetylamino)-N-[[4- (aminocarbonyl)cyclohexyl]methyl]-2,3,4,9-tetrahydro-1H- carbazole-3-carboxamide	<u>136</u>	410	410,515
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(3R)-3-(Acetylamino)-N-[[4- (aminocarbonyl)cyclohexyl]methyl]-2,3,4,9-tetrahydro-1H- carbazole-3-carboxamide	<u>137</u>	410	410,515
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(3S)-3-(Acetylamino)-N-[(1S)-2-amino-2-oxo-1- phenylethyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>138</u>	404	404,4676
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Example 22:

Synthesis takes place on the 0.2 mmol scale in accordance with Examples 18 and 6.

20

Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[(ethylamino)carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>139</u>	505	504.6274
Phenylmethyl [(1S,2S)-2-methyl-1-[[[(3R)-2,3,4,9-tetrahydro-3-[[[1-methylethyl]amino]carbonyl]-1H-carbazol-3-yl]amino]carbonyl]butyl]carbamate	<u>140</u>	519	518.6542
Phenylmethyl [(1S,2S)-2-methyl-1-[[[(3R)-2,3,4,9-tetrahydro-3-[[[2-methylpropyl]amino]carbonyl]-1H-carbazol-3-yl]amino]carbonyl]butyl]carbamate	<u>141</u>	533	532.681
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[2,2-dimethylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>142</u>	547	546.7078
Phenylmethyl [(1S,2S)-2-methyl-1-[[[(3R)-2,3,4,9-tetrahydro-3-[(phenylamino)carbonyl]-1H-carbazol-3-yl]amino]carbonyl]butyl]carbamate	<u>143</u>	553	552.6714
Phenylmethyl [(1S,2S)-2-methyl-1-[[[(3R)-2,3,4,9-tetrahydro-3-[[[phenylmethyl]amino]carbonyl]-1H-carbazol-3-yl]amino]carbonyl]butyl]carbamate	<u>144</u>	567	566.6982
Phenylmethyl [(1S,2S)-2-methyl-1-[[[(3R)-2,3,4,9-tetrahydro-3-[[[2-phenylethyl]amino]carbonyl]-1H-carbazol-3-yl]amino]carbonyl]butyl]carbamate	<u>145</u>	581	580.725
Phenylmethyl [(1S,2S)-2-methyl-1-[[[(3R)-2,3,4,9-tetrahydro-3-[[[3-phenylpropyl]amino]carbonyl]-1H-carbazol-3-yl]amino]carbonyl]butyl]carbamate	<u>146</u>	595	584.7518

Example 23:

- 5 Synthesis takes place on the 0.2 mmol scale by methods A, F, G, I, F, G and O.

Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>147a</u>	606	605.7317
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>147b</u>	606	605.7317
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6-chloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>148a</u>	610	610.151
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6-chloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>148b</u>	610	610.151
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-8-chloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>180a</u>	610	610.151

Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-8-chloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>180b</u>	610	610,151
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-8-(trifluoromethyl)-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>149a</u>	644	643.703
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-8-(trifluoromethyl)-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>149b</u>	644	643.703
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-8-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>150a</u>	590	589.7327
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-8-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>150b</u>	590	589.7327
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-5-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>151a</u>	590	589.7327
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-5-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>151b</u>	590	589.7327
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-7-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>151c</u>	590	589.7327

Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-7-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>151d</u>	590	589.7327
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-5-chloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>152a</u>	610	610.151
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-7-chloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>152b</u>	610	610.151
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-7-chloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>152c</u>	610	610.151
(3R)-3-[[[(1S)-1-(Aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-3-[[[(2S,3S)-3-methyl-1-oxo-2-[[[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1H-carbazole-8-carboxylic acid	<u>153a</u>	620	619.7149
(3S)-3-[[[(1S)-1-(Aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-3-[[[(2S,3S)-3-methyl-1-oxo-2-[[[(phenylmethoxy)carbonyl]amino]pentyl]amino]-1H-carbazole-8-carboxylic acid	<u>153b</u>	620	619.7149
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6-fluoro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>154a</u>	593	593.696
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6-fluoro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>154b</u>	593	593.696
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-6-methoxy-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>155a</u>	605	605.7317

Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-6-methoxy-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>155b</u>	605	605.7317
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-6-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>156a</u>	589	589.7327
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-6-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>156b</u>	589	589.7327
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-6-nitro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>157a</u>	621	620.703
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-6-nitro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>157b</u>	621	620.703
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-4-[(aminoiminomethyl)amino]butyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>158</u>	633	632.7616
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(3-pyridinylacetyl)amino]-1H-carbazole-3-carboxamide	<u>159a</u>	447	447.5361
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(3-pyridinylacetyl)amino]-1H-carbazole-3-carboxamide	<u>159b</u>	447	447.5361
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1-naphthalenylacetyl)amino]-1H-carbazole-3-carboxamide	<u>160a</u>	496	496.6078

(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1-naphthalenylacetyl)amino]-1H-carbazole-3-carboxamide	<u>160b</u>	496	496,6078
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(2-naphthalenylacetyl)amino]-1H-carbazole-3-carboxamide	<u>161a</u>	496	496,6078
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(2-naphthalenylacetyl)amino]-1H-carbazole-3-carboxamide	<u>161b</u>	496	496,6078
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(2,3-dihydro-1H-inden-1-yl)carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>162a</u>	472	472.5858
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(2,3-dihydro-1H-inden-1-yl)carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>162b</u>	472	472.5858
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1H-imidazol-4-ylacetyl)amino]-1H-carbazole-3-carboxamide	<u>163a</u>	436	436.5132
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1H-imidazol-4-ylacetyl)amino]-1H-carbazole-3-carboxamide	<u>163b</u>	436	436.5132
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1H-indol-3-ylacetyl)amino]-1H-carbazole-3-carboxamide	<u>164a</u>	486	485.5849
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1H-indol-3-ylacetyl)amino]-1H-carbazole-3-carboxamide	<u>164b</u>	486	485.5849
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(4-methylphenyl)acetyl]amino]-1H-carbazole-3-carboxamide	<u>165a</u>	461	460.5748
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(4-methylphenyl)acetyl]amino]-1H-carbazole-3-carboxamide	<u>165b</u>	461	460.5748
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[4-(trifluoromethyl)phenyl]acetyl]amino]-1H-carbazole-3-carboxamide	<u>166a</u>	515	514.5451

(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[4-(trifluoromethyl)phenyl]acetyl]amino]-1H-carbazole-3-carboxamide	<u>166b</u>	515	514.5451
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-chlorophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>167a</u>	481	480.9931
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-chlorophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>167b</u>	481	480.9931
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[3-(trifluoromethyl)phenyl]acetyl]amino]-1H-carbazole-3-carboxamide	<u>168a</u>	515	514.5451
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[3-(trifluoromethyl)phenyl]acetyl]amino]-1H-carbazole-3-carboxamide	<u>168b</u>	515	514.5451
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[3-fluorophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>169a</u>	465	464.5381
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[3-fluorophenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>169b</u>	465	464.5381
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[3-methoxyphenyl]acetyl]amino]-1H-carbazole-3-carboxamide	<u>170a</u>	477	476.5738
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[3-methoxyphenyl]acetyl]amino]-1H-carbazole-3-carboxamide	<u>170b</u>	477	476.5738
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[2-methoxyphenyl]acetyl]amino]-1H-carbazole-3-carboxamide	<u>171a</u>	477	476.5738
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[2-methoxyphenyl]acetyl]amino]-1H-carbazole-3-carboxamide	<u>171b</u>	477	476.5738
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[3-(4-fluorophenyl)-1-oxopropyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>172a</u>	479	478.5649

(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[3-(4-fluorophenyl)-1-oxopropyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>172b</u>	479	478.5649
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[3-(3,4-difluorophenyl)-1-oxopropyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>173a</u>	497	496.555
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[3-(3,4-difluorophenyl)-1-oxopropyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>173b</u>	497	496.555
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[3-[3,4-bis(trifluoromethyl)phenyl]-1-oxopropyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>174a</u>	593	592.6057
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[3-[3,4-bis(trifluoromethyl)phenyl]-1-oxopropyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>174b</u>	593	592.6057
N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[4-methoxyphenyl]acetyl]amino]-1H-carbazole-3-carboxamide	<u>175</u>	477	476.5738
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[3-(4-methoxyphenyl)-1-oxopropyl]amino]-1H-carbazole-3-carboxamide	<u>176a</u>	491	490.6006
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[3-(4-methoxyphenyl)-1-oxopropyl]amino]-1H-carbazole-3-carboxamide	<u>176b</u>	491	490.6006
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[3-(2-methoxyphenyl)-1-oxopropyl]amino]-1H-carbazole-3-carboxamide	<u>177a</u>	491	490.6006
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[3-(2-methoxyphenyl)-1-oxopropyl]amino]-1H-carbazole-3-carboxamide	<u>177b</u>	491	490.6006
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[3-(1H-indol-3-yl)-1-oxopropyl]amino]-1H-carbazole-3-carboxamide	<u>178a</u>	500	499.6117
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[3-(1H-indol-3-yl)-1-oxopropyl]amino]-1H-carbazole-3-carboxamide	<u>178b</u>	500	499.6117

(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1-oxo-6-phenylhexyl)amino]-1H-carbazol-3-carboxamide	<u>179a</u>	503	502.6552
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1-oxo-6-phenylhexyl)amino]-1H-carbazol-3-carboxamide	<u>179b</u>	503	502.6552
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[(2S)-2-(aminocarbonyl)-1-pyrrolidinyl]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>181a</u>	574	573.6901
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[(2S)-2-(aminocarbonyl)-1-pyrrolidinyl]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>181b</u>	574	573.6901
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-7,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>182a</u>	645	644.5961
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-7,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>182b</u>	645	644.5961
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-5,8-dimethyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>183a</u>	604	603.7595
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-5,8-dimethyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>183b</u>	604	603.7595
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>184a</u>	645	644.5961
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>184b</u>	645	644.5961

Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6-bromo-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>185a</u>	655	654.602
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6-bromo-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>185b</u>	655	654.602
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazole-3-carboxamide	<u>186a</u>	511	511.0189
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazole-3-carboxamide	<u>186b</u>	511	511.0189
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1R)-2-amino-1-[(4-chlorophenyl)methyl]-2-oxoethyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>187a</u>	658	658.195
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1R)-2-amino-1-[(4-chlorophenyl)methyl]-2-oxoethyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>187b</u>	658	658.195
Phenylmethyl [(1S,2S)-1-[[[3-[[[(3-amino-3-oxopropyl)amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>188</u>	548	547.6523
(2S)-1-[[[(3R)-3-[[[(4-Chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-yl]carbonyl]-2-pyrrolidinecarboxamide	<u>189a</u>	509	509.0031
(2S)-1-[[[(3S)-3-[[[(4-Chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-yl]carbonyl]-2-pyrrolidinecarboxamide	<u>189b</u>	509	509.0031
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(2S)-2-(aminocarbonyl)octahydro-1H-indol-1-yl]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>190a</u>	628	627.7815

Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(2S)-2-(aminocarbonyl)octahydro-1H-indol-1-yl]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>190b</u>	628	627.7815
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(2S,4R)-2-(aminocarbonyl)-4-hydroxy-1-pyrrolidinyl]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>191a</u>	590	589.6891
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(2S,4R)-2-(aminocarbonyl)-4-hydroxy-1-pyrrolidinyl]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>191b</u>	590	589.6891
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2R)-1-(aminocarbonyl)-2-hydroxypropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>291a</u>	578	577.6781
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S,2R)-1-(aminocarbonyl)-2-hydroxypropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>291b</u>	578	577.6781
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(2-amino-2-oxoethyl)amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>292</u>	534	533.6255
Phenylmethyl [(1S,2S)-1-[[[3-[[[2-(aminocarbonyl)phenyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>192</u>	596	595.6963
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-chloro-3-[[[4-pyridinylamino]-carbonyl]amino]phenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>193a</u>	616	616.119
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-chloro-3-[[[4-pyridinylamino]carbonyl]amino]phenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>193b</u>	616	616.119
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-chloro-3-[[[phenylamino]-carbonyl]amino]phenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>194a</u>	615	615.13
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-	<u>194b</u>	615	615.13

chloro-3-[[[(phenylamino)-
carbonyl]amino]phenyl]acetyl]amino]-2,3,4,9-tetrahydro-
1H-carbazole-3-carboxamide

(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-
chloro-3-[[[(phenylmethyl)amino]-
carbonyl]amino]phenyl]acetyl]amino]-2,3,4,9-tetrahydro-
1H-carbazole-3-carboxamide 195a 629 629.157

(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-
chloro-3-[[[(phenylmethyl)amino]carbonyl]amino]-
phenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-
carboxamide 195b 629 629.157

(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-
chloro-3-[(2-pyridinylamino)carbonyl]amino]-
phenyl]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-
carboxamide 196a 616 616.119

(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[4-
chloro-3-[(2-pyridinylamino)carbonyl]amino]phenyl]acetyl]-
amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide 196b 616 616.119

Example 24:

Synthesis takes place on the 0.2 mmol scale by methods
5 A, F, G, I, F, H and O.

(3R)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-
methylpropyl]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-
carboxamide 197a 400 400.4762

(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-
methylpropyl]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-
carboxamide 197b 400 400.4762

3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-
methylpropyl]-6-chloro-2,3,4,9-tetrahydro-1H-carbazole-3-
carboxamide 198 405 404.8955

3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-
methylpropyl]-2,3,4,9-tetrahydro-5-methyl-1H-carbazole-3-
carboxamide 199 769 768.9544

3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-8-methyl-1H-carbazole-3-carboxamide	<u>200</u>	769	769.9544
3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-5-chloro-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>201</u>	810	809.7911
3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-7-chloro-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>202</u>	810	809.7911
(3R)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-6-fluoro-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>203a</u>	388	388.4405
(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-6-fluoro-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>203b</u>	388	388.4405
(3R)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-6-methoxy-1H-carbazole-3-carboxamide	<u>204a</u>	400	400.4762
(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-6-methoxy-1H-carbazole-3-carboxamide	<u>204b</u>	400	400.4762
(3R)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-6-methyl-1H-carbazole-3-carboxamide	<u>205a</u>	384	384.4772
(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-6-methyl-1H-carbazole-3-carboxamide	<u>205b</u>	384	384.4772
(3R)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>206a</u>	370	370.4504
(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>206b</u>	370	370.4504
(3R)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-7,8-dichloro-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>207a</u>	439	439.3406

(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-7,8-dichloro-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>207b</u>	439	439.3406
(3R)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-5,8-dimethyl-1H-carbazole-3-carboxamide	<u>208a</u>	399	398.504
(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-5,8-dimethyl-1H-carbazole-3-carboxamide	<u>208b</u>	399	398.504
(3R)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>209a</u>	439	439.3406
(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>209b</u>	439	439.3406

Example 25:

Synthesis takes place on the 0.2 mmol scale by methods

5 A, F, G, I, F, G, F and O.

(3R)-3-[[[(2S)-2-Amino-5-[(aminoiminomethyl)amino]-1-oxopentyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>210a</u>	485	484.6014
(3S)-3-[[[(2S)-2-Amino-5-[(aminoiminomethyl)amino]-1-oxopentyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>210b</u>	485	484.6014
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[2-(1-piperidinyl)ethyl]amino]acetyl]amino]-1H-carbazole-3-carboxamide	<u>211a</u>	497	496.652
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[2-(1-piperidinyl)ethyl]amino]acetyl]amino]-1H-carbazole-3-carboxamide	<u>211b</u>	497	496.652
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[2-(1H-indol-3-yl)ethyl]amino]acetyl]amino]-1H-carbazole-3-carboxamide	<u>212a</u>	529	528.6534

(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[2-(1H-indol-3-yl)ethyl]amino]acetyl]amino]-1H-carbazole-3-carboxamide	<u>212b</u>	529	528.6534
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(1,3-benzodioxol-5-ylmethyl)amino]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>213a</u>	520	519.5987
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(1,3-benzodioxol-5-ylmethyl)amino]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>213b</u>	520	519.5987
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(2,2-diphenylethyl)amino]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>214a</u>	566	565.7141
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(2,2-diphenylethyl)amino]acetyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>214b</u>	566	565.7141
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[2-[methyl(phenylmethyl)amino]ethyl]amino]acetyl]amino]-1H-carbazole-3-carboxamide	<u>215a</u>	533	532.685
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[2-[methyl(phenylmethyl)amino]ethyl]amino]acetyl]amino]-1H-carbazole-3-carboxamide	<u>215b</u>	533	532.685

Example 26:

Synthesis takes place on the 0.2 mmol scale by methods
 5 A, F, G, I, F, G, F, H and O.

3-[[[Acetyl[2-(1-piperidiny)ethyl]amino]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>216</u>	539	538.8888
(3R)-3-[[[Acetyl[2-[methyl(phenylmethyl)amino]ethyl]amino]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>217a</u>	575	574.7217

(3S)-3-[[[Acetyl(2-methyl(phenylmethyl)amino)ethyl]amino]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>217b</u>	575	574.7217
(3R)-3-[[[Acetyl(2,2-diphenylethyl)amino]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>218a</u>	608	607.7509
(3S)-3-[[[Acetyl(2,2-diphenylethyl)amino]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>218b</u>	608	607.7509
(3R)-3-[[[Acetyl(1,3-benzodioxol-5-ylmethyl)amino]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>219a</u>	562	561.6355
(3S)-3-[[[Acetyl(1,3-benzodioxol-5-ylmethyl)amino]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>219b</u>	562	561.6355
(3R)-3-[[[Acetyl(2-(1H-indol-3-yl)ethyl)amino]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>220a</u>	571	570.6902
(3S)-3-[[[Acetyl(2-(1H-indol-3-yl)ethyl)amino]acetyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>220b</u>	571	570.6902
3-[(2S)-2-(Acetylamino)-5-[(aminoiminomethyl)amino]-1-oxopentyl]amino]-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>221</u>	527	526.6362

Example 27:

Synthesis takes place on the 0.2 mmol scale by methods

5 C, F, G, I, F, G and P.

Phenylmethyl [(1S,2S)-2-methyl-1-[[[(3R)-2,3,4,9-tetrahydro-3-[[[(1S)-2-methyl-1-[(methylamino)carbonyl]propyl]amino]carbonyl]-1H-carbazol-3-yl]amino]carbonyl]butyl]carbamate	<u>222a</u>	589	589.7327
Phenylmethyl [(1S,2S)-2-methyl-1-[[[(3S)-2,3,4,9-tetrahydro-3-[[[(1S)-2-methyl-1-[(methylamino)carbonyl]propyl]amino]carbonyl]-1H-carbazol-3-yl]amino]carbonyl]butyl]carbamate	<u>222b</u>	589	589.7327

Example 28:

Synthesis takes place on the 0.2 mmol scale by methods A, F, G, I, F, J and O.

(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[4-chlorophenyl)sulfonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>223a</u>	503	503.0203
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[4-chlorophenyl)sulfonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>223b</u>	503	503.0203
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(methylsulfonyl)amino]-1H-carbazole-3-carboxamide	<u>224a</u>	407	406.5044
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(methylsulfonyl)amino]-1H-carbazole-3-carboxamide	<u>224b</u>	407	406.5044
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(phenylsulfonyl)amino]-1H-carbazole-3-carboxamide	<u>225a</u>	469	468.5752
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(phenylsulfonyl)amino]-1H-carbazole-3-carboxamide	<u>225b</u>	469	468.5752
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[phenylmethyl)sulfonyl]amino]-1H-carbazole-3-carboxamide	<u>226a</u>	483	482.602
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[phenylmethyl)sulfonyl]amino]-1H-carbazole-3-carboxamide	<u>226b</u>	483	482.602

5

Example 29:

Synthesis takes place on the 0.2 mmol scale by methods A, F, G, I, F, L and O.

3-Phenylpropyl [(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbamate	<u>227a</u>	491	490.8006
3-Phenylpropyl [(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbamate	<u>227b</u>	491	490.8006
Phenylmethyl [(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbamate	<u>228a</u>	463	462.547
Phenylmethyl [(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbamate	<u>228b</u>	463	462.547
Phenyl [(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbamate	<u>229a</u>	449	448.5202
Phenyl [(3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]carbamate	<u>229b</u>	449	448.5202

Example 30:

Synthesis takes place on the 0.2 mmol scale by methods

5 A, F, G, I, F, M and O.

(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(4-nitrophenyl)methyl]amino]-1H-carbazole-3-carboxamide	<u>230a</u>	464	463.5351
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(4-nitrophenyl)methyl]amino]-1H-carbazole-3-carboxamide	<u>230b</u>	464	463.5351
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-(ethylamino)-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>231a</u>	356	356.4672

(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-(ethylamino)-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>231b</u>	356	358.4672
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(2-phenylethyl)amino]-1H-carbazole-3-carboxamide	<u>232a</u>	433	432.5648
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(2-phenylethyl)amino]-1H-carbazole-3-carboxamide	<u>232b</u>	433	432.5648
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(3-phenylpropyl)amino]-1H-carbazole-3-carboxamide	<u>233a</u>	447	446.5916
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(3-phenylpropyl)amino]-1H-carbazole-3-carboxamide	<u>233b</u>	447	446.5916
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[bis(3-phenylpropyl)amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>233c</u>	565	564.7696
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(6-phenylhexyl)amino]-1H-carbazole-3-carboxamide	<u>234a</u>	489	488.672
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(6-phenylhexyl)amino]-1H-carbazole-3-carboxamide	<u>234b</u>	489	488.672
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1-methylethyl)amino]-1H-carbazole-3-carboxamide	<u>235a</u>	370	370.494
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1-methylethyl)amino]-1H-carbazole-3-carboxamide	<u>235b</u>	370	370.494
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1-methylpropyl)amino]-1H-carbazole-3-carboxamide	<u>236a</u>	385	384.5208
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1-methylpropyl)amino]-1H-carbazole-3-carboxamide	<u>236b</u>	385	384.5208

(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(3-methylbutyl)amino]-1H-carbazole-3-carboxamide	<u>237a</u>	399	398.5476
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(3-methylbutyl)amino]-1H-carbazole-3-carboxamide	<u>237b</u>	399	398.5476
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-(methyldamino)-1H-carbazole-3-carboxamide	<u>238a</u>	342	342.4404
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-(methyldamino)-1H-carbazole-3-carboxamide	<u>238b</u>	342	342.4404
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-(dimethylamino)-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>238c</u>	356	356.4672
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-(dimethylamino)-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>238d</u>	356	356.4672

Example 31:

Synthesis takes place on the 0.2 mmol scale by methods

5 A, F, G, I, F, K and O.

(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(methyldamino)carbonyl]amino]-1H-carbazole-3-carboxamide	<u>239a</u>	385	385.4653
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(methyldamino)carbonyl]amino]-1H-carbazole-3-carboxamide	<u>239b</u>	385	385.4653
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(phenyldamino)carbonyl]amino]-1H-carbazole-3-carboxamide	<u>240a</u>	448	447.5361
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(phenyldamino)carbonyl]amino]-1H-carbazole-3-carboxamide	<u>240b</u>	448	447.5361

(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(phenylmethyl)amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>241a</u>	462	461.5629
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(phenylmethyl)amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>241b</u>	462	461.5629
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(2-phenylethyl)amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>242a</u>	476	475.5897
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(2-phenylethyl)amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>242b</u>	476	475.5897
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(cyclohexylamino)carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>243a</u>	454	453.5835
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(cyclohexylamino)carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>243b</u>	454	453.5835
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(1-methylethyl)amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>244a</u>	414	413.5189
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(1-methylethyl)amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>244b</u>	414	413.5189
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(1-methylpropyl)amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>245a</u>	428	427.5457
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(1-methylpropyl)amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>245b</u>	428	427.5457
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(1R)-1-phenylethyl]amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>246a</u>	476	475.5897
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(1R)-1-phenylethyl]amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>246b</u>	476	475.5897

(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)amino]carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>247a</u>	482	481.9812
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)amino]carbonyl]amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>247b</u>	482	481.9812
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(1S)-1-phenylethyl]amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>248a</u>	476	475.5897
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[[(1S)-1-phenylethyl]amino]carbonyl]amino]-1H-carbazole-3-carboxamide	<u>248b</u>	476	475.5897

Example 32:

Synthesis takes place on the 0.2 mmol scale by methods

5 A, F, G, I, F, G, N and O.

Ethyl (3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-3-[[[(4-chlorophenyl)acetyl]amino]-1,2,3,4-tetrahydro-9H-carbazole-9-acetate	<u>249a</u>	567	567.0825
Ethyl (3S)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-3-[[[(4-chlorophenyl)acetyl]amino]-1,2,3,4-tetrahydro-9H-carbazole-9-acetate	<u>249b</u>	567	567.0825
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(3-phenylpropyl)-1H-carbazole-3-carboxamide	<u>250a</u>	599	599.1711
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(3-phenylpropyl)-1H-carbazole-3-carboxamide	<u>250b</u>	599	599.1711
(3R)-3-[[[(1S)-1-(Aminocarbonyl)-2-methylpropyl]amino]carbonyl]-3-[[[(4-chlorophenyl)acetyl]amino]-1,2,3,4-tetrahydro-9H-carbazole-9-acetic acid	<u>251a</u>	539	539.0289

(3S)-3-[[[(1S)-1-(Aminocarbonyl)-2-methylpropyl]amino]carbonyl]-3-[[[(4-chlorophenyl)acetyl]amino]-1,2,3,4-tetrahydro-9H-carbazole-9-acetic acid	<u>251b</u>	539	539,0289
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(3-methylbutyl)-1H-carbazole-3-carboxamide	<u>252a</u>	551	551.1271
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(3-methylbutyl)-1H-carbazole-3-carboxamide	<u>252b</u>	551	551.1271
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(4-pyridinylmethyl)-1H-carbazole-3-carboxamide	<u>253a</u>	572	572.1056
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(4-pyridinylmethyl)-1H-carbazole-3-carboxamide	<u>253b</u>	572	572.1058
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(3-pyridinylmethyl)-1H-carbazole-3-carboxamide	<u>254a</u>	572	572.1056
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(3-pyridinylmethyl)-1H-carbazole-3-carboxamide	<u>254b</u>	572	572.1056
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(2-naphthalenylmethyl)-1H-carbazole-3-carboxamide	<u>255a</u>	621	621.1773
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(2-naphthalenylmethyl)-1H-carbazole-3-carboxamide	<u>255b</u>	621	621.1773
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(2-methylpropyl)-1H-carbazole-3-carboxamide	<u>256a</u>	537	537.1003
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(2-methylpropyl)-1H-carbazole-3-carboxamide	<u>256b</u>	537	537.1003
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-9-(2-phenylethyl)-1H-carbazole-3-carboxamide	<u>257a</u>	585	585.1443

(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[4-chlorophenyl]acetyl]amino]-2,3,4,9-tetrahydro-9-(2-phenylethyl)-1H-carbazole-3-carboxamide	<u>257b</u>	585	585.1443
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[4-chlorophenyl]acetyl]amino]-9-ethyl-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>258a</u>	509	509.0467
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[4-chlorophenyl]acetyl]amino]-9-ethyl-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>258b</u>	509	509.0467
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[4-chlorophenyl]acetyl]amino]-9-(cyclohexylmethyl)-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>259a</u>	577	577.1649
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[4-chlorophenyl]acetyl]amino]-9-(cyclohexylmethyl)-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>259b</u>	577	577.1649
(3R)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[4-chlorophenyl]acetyl]amino]-9-[(2,6-difluorophenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>260a</u>	607	607.0977
(3S)-N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-3-[[4-chlorophenyl]acetyl]amino]-9-[(2,6-difluorophenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>260b</u>	607	607.0977

Example 33:

Synthesis takes place on the 0.2 mmol scale by methods

5 A, F, G, I, F, H, N and O.

(3R)-3-(Acetyl amino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-9-(3-phenylpropyl)-1H-carbazole-3-carboxamide	<u>261a</u>	489	488.6284
(3S)-3-(Acetyl amino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-9-(3-phenylpropyl)-1H-carbazole-3-carboxamide	<u>261b</u>	489	488.6284
(3R)-3-(Acetyl amino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-9-(3-methylbutyl)-1H-carbazole-3-carboxamide	<u>262a</u>	441	440.5844

(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-9-(3-methylbutyl)-1H-carbazole-3-carboxamide	<u>262b</u>	441	440.5844
(3R)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-9-(2-naphthalenylmethyl)-1H-carbazole-3-carboxamide	<u>263a</u>	511	510.6346
(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-9-(2-naphthalenylmethyl)-1H-carbazole-3-carboxamide	<u>263b</u>	511	510.6346
3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-9-(1-naphthalenylmethyl)-1H-carbazole-3-carboxamide	<u>264</u>	511	510.6346
3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-9-(cyclohexylmethyl)-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>265</u>	457	466.6222
(3R)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-9-(2-methylpropyl)-1H-carbazole-3-carboxamide	<u>266a</u>	427	426.5576
(3S)-3-(Acetylamino)-N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-9-(2-methylpropyl)-1H-carbazole-3-carboxamide	<u>266b</u>	427	426.5576

Example 34:

Synthesis takes place on the 0.2 mmol scale by methods
 5 D, F, G, I, F, O and subsequent coupling in accordance with Example 6.

Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>267a</u>	563	562.7068
Phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>267b</u>	563	562.7068

10 *Example 35:*

Ethyl 2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazole-3-carboxylate 268

10 mmol (1.6 ml) of ethyl 4-oxocyclohexanecarboxylate,
 15 25 mmol (1.4 ml) of glycol and 10 μ mol of pTsoH are

refluxed in dry toluene with a water trap for 24 h. The solvent is removed and the residue is taken up in ethyl acetate/water. The organic phase is washed with water, dried and evaporated to dryness. The product is
5 distilled in a Kugelrohr apparatus under high vacuum at 120°C and 0.03 mbar.

Yield: 1.52 g of 4-ethyl 1,4-dioxaspiro[4,5]decane-8-carboxylate 269.

10 85 µl of diisopropylamine in 500 µl of dry THF are added dropwise to 0.6 mmol of a 1.6 molar solution of butyllithium in heptane at -20°C under argon and then stirred for 10 min. After cooling to -70°C, 0.5 mmol
15 (107 mg) of 269 in 200 µl of dry THF are added dropwise, allowed to reach 0°C over the course of one hour and stirred for a further 30 min. After cooling to -70°C, 0.7 mmol (106 µl) of 1-bromo-3-phenylpropane in 300 µl of dry THF are added, and the mixture is stirred for 30 min. It is allowed to reach RT and then stirred
20 for 1 hour. The saturated NH₄Cl solution and n-hexane are cautiously added to the organic phase, which is stirred for 10 min. The organic phase is separated and washed with water. Filtration through a Whatman filter is followed by evaporation to dryness.

25 Yield: 165 mg of ethyl 8-(3-phenylpropyl)-1,4-dioxaspiro[4,5]decane-8-carboxylate 270.

0.6 mmol (200 mg) of 270 are taken up in 25 ml of acetone/0.1 M HCl 1:1 and stirred with catalytic
30 amounts of pTsOH at 50°C for 48 h. The acetone is stripped off in a rotary evaporator, and the precipitated product is filtered off, washed with water and dried.

Yield: 156 mg of ethyl 4-oxo-8-(3-phenylpropyl)cyclo-
35 hexanecarboxylate 271.

The indolization takes place as described in Example 1 using phenylhydrazine.

Yield after evaporation and preparative HPLC: 65 mg of ethyl 2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazole-3-carboxylate 268.

5 ES-MS: 362 ($M+H^+$)

80 mg of ethyl 6,8-dichloro-2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazole-3-carboxylate 272 are prepared analogously using 2,4-dichlorophenylhydrazine.

10

ES-MS: 430 ($M+H^+$)

Example 36:

2,3,4,9-Tetrahydro-3-(3-phenylpropyl)-1H-carbazole-3-carboxylic acid 273

15

3.94 mmol (1.31 g) of 269 are stirred in 50 ml of methanol and 30 ml of 50% sodium hydroxide solution at 60°C for 4 h. The mixture is acidified with dilute HCl and extracted with ether. Drying with Na_2SO_4 and evaporation affords 1.02 g (85%) of white solid 8-(3-phenylpropyl)-1,4-dioxaspiro[4,5]decane-8-carboxylic acid 274.

20

65 mg of 274 are first deprotected with HCl and then reacted with phenylhydrazine for the indolization as described for 270 and 271.

Yield after evaporation and preparative HPLC: 15 mg of 273.

30

ES-MS: 334 ($M+H^+$)

35

39 mg of 6,8-dichloro-2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazole-3-carboxylic acid 275 are prepared analogously using 2,4-dichlorophenylhydrazine.

ES-MS: 478 ($M+H^+$)

Example 37:

2,3,4,9-Tetrahydro-*N*-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-3-(3-phenylpropyl)-1*H*-carbazole-3-carboxamide 276

- 5 0.66 mmol (200 mg) of 274 are reacted with 1.5 equivalents of valinol in analogy to Example 6. 277 mg of white solid *N*-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-8-(3-phenylpropyl)-1,4-dioxaspiro[4,5]-decane-8-carboxamide 277 are obtained.

10

Then 0.3 mmol (117 mg) of 277 are first deprotected with HCl and subsequently reacted with phenylhydrazine for the indolization as described for 270 and 271. Yield after evaporation and preparative HPLC: 15 mg of 276.

15

ES-MS: 418 ($M+H^+$)

- 25 mg of 6,8-dichloro-2,3,4,9-tetrahydro-*N*-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-3-(3-phenylpropyl)-1*H*-carbazole-3-carboxamide 278 are prepared analogously using 2,4-dichlorophenylhydrazine.

20

ES-MS: 486 ($M+H^+$)

25

Example 38:

2,3,4,9-Tetrahydro-3-(3-phenylpropyl)-*N*-(2-pyridinylmethyl)-1*H*-carbazole-3-methanamine 279

- 30 54 ml of a 1 M solution of $LiAlH_4$ in dry THF are cautiously added to a solution of 18 mmol (6 g) of 270 in 250 ml of dry THF under argon at room temperature. After heating to reflux for 3 h, cautious hydrolysis is carried out with 300 ml of saturated NH_4Cl solution, and
- 35 250 ml of ether are added. The aluminum salts are filtered off and washed with ether. Drying of the ether phase with Na_2SO_4 and evaporation of the solvent afford 3.4 g of 8-(3-phenylpropyl)-1,4-dioxaspiro[4,5]decane-8-methanol 280.

5.86 mmol (1.7 g) of 280 are dissolved in 60 ml of dry DCM and 20 ml of dry DMSO. Under nitrogen at room temperature, firstly 44 mmol (6.1 ml) of TEA and then
5 cautiously 17.6 mmol (2.8 g) of SO₃-pyridine complex are added, and the mixture is stirred for one hour. Subsequently 200 ml of saturated NH₄Cl solution are added and extraction is carried out with 150 ml of ether. Drying of the ether phase with Na₂SO₄ and
10 evaporation of the solvent afford 1.9 g of 8-(3-phenylpropyl)-1,4-dioxaspiro[4,5]decane-8-carbaldehyde 281 as colorless oil.

0.719 mmol of sodium triacetoxyborohydride are added to
15 a mixture of 0.359 mmol (103 mg) of 281 and 0.359 mmol (37 ml) of 2-pyridinemethanamine in 2.5 ml of 1,2-dichloroethane. The mixture is stirred under N₂ at room temperature for 3 h. Saturated NaHCO₃ solution is added, and the mixture is extracted with ether. The dried and
20 evaporated ether extract affords 101 mg (76%) of white solid N-[8-(3-phenylpropyl)-1,4-dioxaspiro[4,5]dec-8-yl]-2-pyridinemethanamine 282.

Subsequently, 101 mg of 282 are first deprotected with
25 HCl and then reacted with phenylhydrazine for the indolization as described for 270 and 271. Yield after evaporation and preparation HPLC: 71 mg of 279.

ES-MS: 410 (M+H⁺)

54 mg of 6,8-dichloro-2,3,4,9-tetrahydro-3-(3-phenyl-
30 propyl)-N-(2-pyridinylmethyl)-1H-carbazole-3-methanamine 283 are prepared analogously using 2,4-dichlorophenylhydrazine.

ES-MS: 478 (M+H⁺)

35

Example 39:

(2S)-3-Methyl-2-[[[2,3,4,9-tetrahydro-3-(3-phenyl-
propyl)-1H-carbazol-3-yl]methyl]amino]-1-butanol 284

0.368 mmol (106 mg) of 281 and 0.368 mmol (38 mg) of valinol are dissolved in 1.5 ml of dry methanol and stirred at room temperature for 30 min. After cooling to 0°C, 0.557 mmol (21 mg) of NaBH₄ are added and stirred at room temperature for 1 h. 0.437 mmol (25 µl) of acetic acid is added, and stirring is continued at pH 6 for 2 h. Saturated NaHCO₃ solution is added, and the mixture is extracted with ether. Drying of the organic phase with Na₂SO₄ and evaporation affords 106 mg (77%) of colorless oil for 270 and 271.

Deprotection and indolization are then carried out as described for 270 and 271. Yield after evaporation and preparative HPLC: 18 mg of white solid 284.

ES-MS: 405 (M+H⁺)

17 mg of (2S)-2-[[[6,8-dichloro-2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazol-3-yl]methyl]amino]-3-methyl-1-butanol 286 are prepared analogously using 2,4-dichlorophenylhydrazine. ES-MS: 473 (M+H⁺)

Example 40:

2,3,4,9-Tetrahydro-3-(3-phenylpropyl)-O-(4-pyridinyl-methyl)-1H-carbazole-3-methanol 287

0.689 mmol of NaH (as 55% suspension in mineral oil) are added to a solution of 0.344 mmol (100 mg) of 280 in 10 ml of dry DMF at 0°C under an N₂ atmosphere. The mixture is allowed to reach room temperature and is stirred for 30 min. 1.377 mmol of 4-(chloromethyl)pyridine are added, and the mixture is stirred at 95-100°C overnight. Cooling to room temperature is followed by hydrolysis with 2 ml of water and extraction with ether. Drying of the solvent and evaporation affords 115 mg of yellow oil 288.

Deprotection and indolization are then carried out as described for 270 and 271. Yield after evaporation and preparative HPLC: 14 mg of white solid 287.

ES-MS: 411 ($M+H^+$)

5

Example 41:

Ethyl 3-[2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazol-3-yl]-2-propenoate 289

- 10 0.347 mmol of 281 in 0.5 ml of THF are added dropwise to a solution of 0.378 mmol of ethyl (triphenylphosphoranylidene)acetate in 1 ml of absolute THF while cooling in ice. After the addition is complete, the mixture is allowed to warm to room
15 temperature and is stirred for a further 2 days. It is then hydrolyzed with water and extracted with ether.
Na₂SO₄ is used for drying, phosphane oxide and desiccant are filtered off, and the solvent is removed. Yield 80%
of ethyl 3-[8-(3-phenylpropyl)-1,4-dioxaspiro[4,5]dec-
20 8-yl]-2-propenoate 290.

Deprotection and indolization are then carried out as described for 270 and 271.

- 25 Yield after evaporation and preparative HPLC: 9 mg of white solid 289.

ES-MS: 388 ($M+H^+$)

- 30 In addition, the compounds of the invention Nos. 293 to 300, 302 and 304 to 306, which are covered by the general formula (I), are obtained on the 0.2 mmol scale by methods A, F, G, F, G and O, the compound 301 by methods B, F, G, F, G and O, and the compound 303 by methods A, F, G, F, G, F, L and O.

<u>Compound name</u>	<u>Number</u>	<u>M_{find}</u>	<u>M_{calc}</u>
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6,8-difluoro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>293</u>	612	611.6861
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-8-methoxy-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>294</u>	620	619.7585
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>295</u>	659	658.6229
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-3-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>296</u>	659	658.6229
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-cyclohexylethyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>297</u>	699	698.6875
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2,2-dimethylpropyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>298</u>	659	658.6229
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-3-phenylpropyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>299</u>	707	706.6669
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-cyclohexylmethyl]carbamate	<u>300</u>	685	684.6607

Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2S)-1-(carboxy)-2-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>301</u>	660	659.607
Phenylmethyl [(1S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-(4-hydroxyphenyl)ethyl]carbamate	<u>302</u>	709	708.6391
Phenylmethyl [(1S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-3-(4-hydroxyphenyl)propyl]carbamate	<u>303</u>	723	722.6659
Phenylmethyl [(1S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-3-phenylpropyl]carbamate	<u>304</u>	707	706.6669
Phenylmethyl [(1S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-3-methylbutyl]carbamate	<u>305</u>	659	658.6229
Phenylmethyl [(1S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-3-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-3-methylbutyl]carbamate	<u>306</u>	659	658.6229

III Demonstration of the GnRH-antagonistic effect of compounds (I) of the invention

5 Materials:

Buserelin is purchased from Welding (Frankfurt/Main, Germany). The compound is labeled with ^{125}I by using the chloramine T method and Na^{125}I (4000 Ci/mmol; Amersham-Buchler, Brunswick, Germany). The labeled substance is purified by reverse phase HPLC on a Spherisorb ODS II column (250 x 4 mm, particle size 3 μm) by elution with 50% acetonitrile/0.15% trifluoroacetic acid at a flow rate of 0.5 ml/min. The specific activity is 2000 Ci/mmol.

All other chemicals are purchased from commercial source in the highest available purity.

5 Cell culture:

Alpha T3-1 cells (Bilezikjian et al., *Mol. Endocrinol* 5 (1991), 347-355) are cultivated in DMEM medium (Gibco-BRL, Eggenstein-Lepoldshafen, Germany) with penicillin (100 I.U./ml), streptomycin (0.1 mg/ml) and glutamine (0.01 mol/l) and 10% fetal calf serum (FCS; PAA Laboratories, Coelbe, Germany) on plastic tissue culture plates (Nunc, 245 x 245 x 20 mm). CHO-3 cells (Schmid et al., *J. Biol. Chem.* 275 (2000), 9193-9200) are cultivated under identical conditions apart from the use of Ham's F12 medium (Gibco-BRL).

10 confluent cell culture plates are washed twice with 50 ml of phosphate-buffered saline (PBS). The cells are harvested by scraping off with a rubber policeman into 20 5 ml of PBS and sedimented by centrifugation at 800 rpm for 10 min in a laboratory centrifuge (Heraeus). The cell pellet is resuspended in 5 ml of 0.25 mol/l sucrose/0.01 mol/l triethanolamine, pH 7.4. The cells are lysed by three cycles of freezing in dry 25 ice/ethanol bath and thawing at room temperature. The lysate is centrifuged at 900 rpm for 10 min, and the sediment is discarded. The supernatant is centrifuged at 18 000 rpm in a Sorvall SS34 rotor for 30 min. The pellet (cell membranes) is suspended in 5 ml of assay 30 buffer (0.25 mol/l sucrose, 0.01 mol/l triethanolamine, pH 7.5, 1 mg/ml ovalbumin) in a Potter, and stored in 200 µl aliquots at -20°C. Protein is determined by the method of Bradford (*Anal. Biochem.* 72 (1976), 248-254).

35 Receptor assay:

Binding studies for competition plots are carried out as triplicates. A test sample contains 60 µl of cell membrane suspension (10 µg of protein for αT3-1-cells or 40 µg of protein for CHO3 cells), 20 µl of ¹²⁵I

- labeled Buserelin (100 000 ipm per sample for competition plots and between 1500 and 200 000 ipm for saturation experiments) and 20 μ l of test buffer or test compound solution. The test compounds are dissolved in distilled water or 50% ethanol. Serial dilutions (5×10^{-6} mol/l to 5×10^{-12} mol/l) are prepared in test buffer. The nonspecific binding is determined in the presence of an excess of an unlabeled Buserelin (10^{-6} mol/l). The test samples are incubated at room temperature for 30 min. Bound and free ligand are separated by filtration (Whatman GF/C filter 2.5 cm diameter) using an Amicon 10x collecting apparatus and washed twice with 5 ml of 0.02 mol/l Tris/HCl, pH 7.4. The filters are moistened with 0.3% polyethyleneimine (Serva, Heidelberg, Germany) for 30 min in order to reduce the nonspecific binding. The radioactivity retained by the filters is determined in a 5-channel gamma counter (Wallac-LKB 1470 Wizard).
- The IC_{50} values obtained for the preferred compounds, as defined above, are indicated in the table which follows.

<u>Compound Name</u>	<u>Example No.</u>	<u>hGnRH receptor IC_{50} [M]</u>	<u>Ca²⁺ release human IC_{50} [M]</u>
N-[[(3R)-2,3,4,9-Tetrahydro-3-[(1-oxo-2,3-diphenylpropyl)-amino]-1H-carbazol-3-yl]-carbonyl]-L-valyl-L-aspartamide	<u>18</u>	0.0000009	0.000005
(3S)-N-[(1S)-1-(Amino-carbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1H-indol-3-ylacetyl)amino]-1H-carbazole-3-carboxamide	<u>164b</u>	0.000006	0.0000065
(3S)-N-[(1S)-1-(Amino-carbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(2-naphthalinylacetyl)amino]-1H-carbazole-3-carboxamide	<u>161b</u>	0.0000037	0.0000036

N-[[[(3R)-2,3,4,9-Tetrahydro-3-[[[(2S,3S)-3-methyl-1-oxo-2-[(1-oxo-3-phenylpropyl)amino]pentyl]amino]-1H-carbazol-3-yl]carbonyl]-L-valyl-L-aspartamide	<u>22</u>	0.000002	0.000001
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2S)-1-(amino-carbonyl)-2-methylbutyl]-amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>64</u>	0.0000017	0.0000015
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-[[[4-(aminocarbonyl)phenyl]amino]-carbonyl]-2-methylpropyl]-amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>45</u>	0.0000003	0.000001
Phenylmethyl [(1S,2S)-2-methyl-1-[[[(3R)-2,3,4,9-tetrahydro-3-[[[(1S)-2-methyl-1-[(methylamino)carbonyl]-propyl]amino]carbonyl]-1H-carbazol-3-yl]amino]carbonyl]-butyl]carbamate	<u>222a</u>	0.0000025	0.000003
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(amino-carbonyl)-2-methylpropyl]-amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>58</u>	0.0000003	0.00000037
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(2S)-2-(amino-carbonyl)-1-pyrrolidinyl]-carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]-carbonyl]-2-methylbutyl]-carbamate	<u>181a</u>	0.0000007	0.000003
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(2S)-2-(amino-carbonyl)octahydro-1H-indol-1-yl]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>190a</u>	0.000002	0.0000005
2,3,4,9-Tetrahydro-3-(3-phenylpropyl)-N-(2-pyridinylmethyl)-1H-carbazole-3-methanamine	<u>279</u>	0.000002	0.000003

(2S)-3-Methyl-2-[[[2,3,4,9-tetrahydro-3-(3-phenylpropyl-1H-carbazol-3-yl)methyl]-amino]-1-butanol	<u>284</u>	0.000007	0.000007
N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[4-methoxyphenyl]acetyl]amino-1H-carbazole-3-carboxamide	<u>175</u>	0.000008	0.0000018
(3R)-N-[(1S)-1-(Amino-carbonyl)-2-methylpropyl]-3-[[3-bromophenyl]acetyl]-amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>96</u>	0.000004	0.000003
(3R)-N-[(1S)-1-(Amino-carbonyl)-2-methylpropyl]-3-[[4-fluorophenyl]acetyl]-amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>91</u>	0.0000024	0.000002
(3R)-N-[(1S)-1-(Amino-carbonyl)-2-methylpropyl]-3-[[4-chlorophenyl]acetyl]-amino]-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide	<u>167a</u>	0.000001	0.0000026
(3R)-N-[(1S)-1-(Amino-carbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(6-phenylhexyl)amino]-1H-carbazole-3-carboxamide	<u>234a</u>	0.000009	0.000001
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(amino-carbonyl)-2-methylpropyl]-amino]carbonyl]-2,3,4,9-tetrahydro-8-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>150a</u>	0.00000011	0.00000028
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(amino-carbonyl)-2-methylpropyl]-amino]carbonyl]-6-chloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>148a</u>	0.00000008	0.00000014
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(amino-carbonyl)-2-methylpropyl]-amino]carbonyl]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>147a</u>	0.000000076	0.00000025

Phenylmethyl [(1S,2S)-1- [[[(3R)-3-[[[(1S)-1-(amino- carbonyl)-2-methylpropyl]- amino]carbonyl]-6,8-dichloro- 2,3,4,9-tetrahydro-1H- carbazol-3-yl]amino]carbonyl]- 2-methylbutyl]carbamate	<u>184a</u>	0.000000015	0.000000045
Phenylmethyl [(1S,2S)-1- [[[(3R)-3-[[[(1S)-1-(hydroxy- methyl)-2-methylpropyl]amino]- carbonyl]-2,3,4,9-tetrahydro- 1H-carbazol-3-yl]amino]- carbonyl]-2-methylbutyl]- carbamate	<u>267a</u>	0.00000004	0.00000005
(2S)-1-[[[(3R)-3-[[[(4-Chloro- phenyl)acetyl]amino]-2,3,4,9- tetrahydro-8-methoxy-1H- carbazol-3-yl]carbonyl]-2- pyrrolidine carboxamide	<u>189a</u>	0.00000007	0.00000005
6,8-Dichloro-2,3,4,9-tetra- hydro-3-(3-phenylpropyl)-N-(2- pyridinylmethyl)-1H-carbazole- 3-methanamine	<u>283</u>	0.0000001	0.0000003

The compounds of numbers 293 to 306 are tested by the methods indicated below:

5 Receptor binding assay

Materials:

¹²⁵I-Triptorelin [¹²⁵I-(D)-Trp6-GnRH] is purchased from Biotrend (Cologne, Germany). The specific activity is 10 in each case 2.13 Ci/mmol. All other chemicals are purchased from commercial sources in the highest purity available.

Cell culture:

15 Transfected LTK' cells (ATCC No. CCL-1.3) are cultivated in DMEM medium (Invitrogen Life Technologies, Germany) with penicillin (100 I.U./ml), streptomycin (0.1 mg/ml) and glutamine (0.01 mol/l) and 10% fetal calf serum (FCS; Invitrogen Life Technologies, Germany) on plastic tissue culture plates 20 (Nunc, Germany, 245 x 245 x 20 mm).

Testing:

80% confluent cell culture plates are washed twice with 50 ml of phosphate-buffered saline (PBS) and then detached with 0.01 M EDTA solution. The cells are pelleted by centrifugation at 200xg for 5 min in a laboratory centrifuge (Kendro, Germany). The cell pellet is resuspended in 3 ml of binding medium (DMEM; 10 mM Hepes; 0.5% BSA; 0.1% NaN₃; 1 g/l Bacitracin (add fresh, stock 100x); 0.1 g/l SBTI (add fresh, stock 1000x) and the cell count is determined by Trypan blue staining in a Neubauer counting chamber. The cell suspension is adjusted with binding medium to a concentration of 5×10^5 cells/0.05 ml.

Binding studies for competition plots are carried out as duplicates. The test substances are employed as 10 mM DMSO solutions. They are diluted to 4 times the final concentration employed with binding medium. 25 µl of the substance dilution are mixed with 25 µl of tracer solution (¹²⁵I-triptorelin). The tracer concentration is adjusted to approx. 50 000 cpm (measured in a Cobra II, γ counter, PE Lief Science, Germany) in the final reaction volume of 100 µl.

200 µl of silicone/liquid paraffin mixture (84%:16%) are introduced into 650 µl conical tubes (Roth, Germany). 50 µl of the cell suspension are pipetted thereon, followed by 50 µl of the test substance/tracer mixture. The tubes are capped and incubated with vertical rotation in an incubator at 37°C for 60 min.

After incubation, the samples are centrifuged in a centrifuge (Kendro, Germany) at 900 rpm and subsequently shock-frozen in liquid N₂. The tip with the cell pellet is cut off and transferred into prepared counting vials (Roth, Germany). The remainder of the conical tube with the remaining supernatant is likewise transferred into a counting vial. The measurement takes place in a γ counter for 1 min/sample.

Evaluation of the samples takes place after calculation of the specific binding compared with untreated cells, after subtraction of the nonspecific binding (excess of

unlabeled ligand, 1 μ m) by means of GraphPad Prism (GraphPad Software Inc., USA).

Functional reporter gene assay

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Materials:

All chemicals are purchased from commercial sources in the highest purity available.

10 Cell culture:

Stably transfected LTK cells (ATCC No. CCL-1.3) which harbor the GnRH receptor and have heterologous expression of cAMP-responsive elements and a CMV minimal promoter-driven luciferase reporter gene are employed to carry out functional investigations.

15

The cells are cultivated in DMEM medium (Invitrogen Life Technologies, Germany) with penicillin (100 I.U./ml), streptomycin (0.1 mg/ml) and glutamine (0.01 mol/l) and 10% fetal calf serum (FCS; Invitrogen Life Technologies, Germany) on plastic tissue culture plates (Nunc, Germany, 245 x 245 x 20 mm).

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Testing:

80% confluent cell culture plates are washed twice with 50 ml of phosphate-buffered saline (PBS) and then detached with trypsin EDTA solution (Invitrogen Life Technologies, Germany). The cells are pelleted by centrifugation at 200xg for 5 min in a laboratory centrifuge (Kendro, Germany). The cell pellet is resuspended in 3 ml of assay medium (Invitrogen Life Technologies, Germany) with penicillin (100 I.U./ml), streptomycin (0.1 mg/ml) and glutamine (0.01 mol/l) and 10% fetal calf serum (FCS; Invitrogen Life Technologies, Germany), and the cell count is determined by Trypan blue staining in a Neubauer counting chamber. The cell suspension is adjusted to a concentration of 1×10^4 cells/100 μ l with assay medium. The cells are set out on white 96-well microtiter

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plates (Costar, Germany) and incubated in an incubator for 18 h.

To carry out the test, test substances are diluted as
 5 10 mM DMSO solutions in assay medium to 6 times the final concentration employed. 25 µl of the test substance are added to 100 µl of cells and incubated at 37°C, 5% CO₂ for 60 min.

10 Triptorelin (D-Trp6-GnRH)/Rolipram solution (6 nM/6 µM) is then added, followed by incubation again at 37°C, 5% CO₂ for 6 h.

Incubation is followed by addition of 50 µl of lysis/detection buffer (LucLite, PE Life Science) and measurement in a Lumistar luminometer (BMG
 15 Labtechnologies GmbH, Germany).

Evaluation of the samples takes place after calculation of the inhibition compared with untreated stimulated cells, after subtraction of the unstimulated control, by means of GraphPad Prism (GraphPad Software Inc.,
 20 USA) or alternatively by means of OMMM (Accelrys, Germany) software.

The EC₅₀ values obtained for compounds 293 to 306 are indicated in the table below.

25

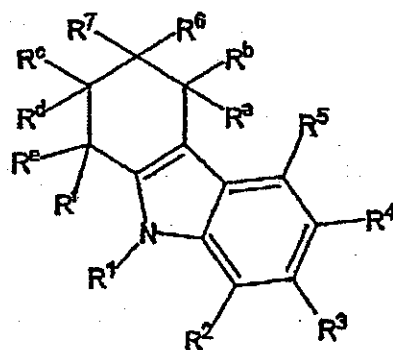
<u>Compound Name</u>	<u>Example No.</u>	<u>Functional human EC₅₀ [M]</u>	<u>Human binding triptorelin EC₅₀ [M]</u>
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6,8-difluoro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>293</u>	0.000000762	0.000000332
Phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-8-methoxy-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate	<u>294</u>	0.000000089	0.000000036

Phenylmethyl [(1S,2S)-1- [[[(3R)-3-[[[(1S,2S)-1- (aminocarbonyl)-2-methyl- butyl]amino]carbonyl]-6,8- dichloro-2,3,4,9-tetra- hydro-1H-carbazol-3- yl]amino]carbonyl]-2- methylbutyl]carbamate	<u>295</u>	0.000000007	0.000000018
Phenylmethyl [(1S,2S)-1- [[[(3R)-3-[[[(1S)-1- (aminocarbonyl)-3-methyl- butyl]amino]carbonyl]-6,8- dichloro-2,3,4,9-tetra- hydro-1H-carbazol-3- yl]amino]carbonyl]-2- methylbutyl]carbamate	<u>296</u>	0.000000014	0.000000022
Phenylmethyl [(1S,2S)-1- [[[(3R)-3-[[[(1S)-1- (aminocarbonyl)-2-cyclo- hexylethyl]amino]carbonyl]- 6,8-dichloro-2,3,4,9- tetrahydro-1H-carbazol-3- yl]amino]carbonyl]-2- methylbutyl]carbamate	<u>297</u>	0.000000284	0.000000482
Phenylmethyl [(1S,2S)-1- [[[(3R)-3-[[[(1S)-1- (aminocarbonyl)-2,2- dimethylpropyl]amino]- carbonyl]-6,8-dichloro- 2,3,4,9-tetrahydro-1H- carbazol-3-yl]amino]- carbonyl]-2-methylbutyl]- carbamate	<u>298</u>		0.000000288
Phenylmethyl [(1S,2S)-1- [[[(3R)-3-[[[(1S)-1- (aminocarbonyl)-3-phenyl- propyl]amino]carbonyl]- 6,8-dichloro-2,3,4,9- tetrahydro-1H-carbazol-3- yl]amino]carbonyl]-2- methylbutyl]carbamate	<u>299</u>	0.000001497	0.000001307
Phenylmethyl [(1S,2S)-1- [[[(3R)-3-[[[(1S)-1- (aminocarbonyl)-2-methyl- butyl]amino]carbonyl]-6,8- dichloro-2,3,4,9-tetra- hydro-1H-carbazol-3-yl]- amino]carbonyl]-2-cyclo- hexylmethyl]carbamate	<u>300</u>	0.000000017	0.000000023

Phenylmethyl [(1S,2S)-1- [[[(3R)-3-[[[(1S,2S)-1- (carboxy)-2-methylbutyl]- amino]carbonyl]-6,8- dichloro-2,3,4,9-tetra- hydro-1H-carbazol-3-yl]- amino]carbonyl]-2- methylbutyl]carbamate	<u>301</u>	0.000000176	0.000000538
Phenylmethyl [(1S)-1- [[[(3R)-3-[[[(1S,2S)-1- (aminocarbonyl)-2-methyl- butyl]amino]carbonyl]-6,8- dichloro-2,3,4,9-tetra- hydro-1H-carbazol-3-yl]- amino]carbonyl]-2-(4- hydroxyphenyl)ethyl]- carbamate	<u>302</u>	0.000000324	0.000000475
Phenylmethyl [(1S)-1- [[[(3R)-3-[[[(1S,2S)-1- (aminocarbonyl)-2-methyl- butyl]amino]carbonyl]-6,8- dichloro-2,3,4,9-tetra- hydro-1H-carbazol-3-yl]- amino]carbonyl]-3-(4- hydroxyphenyl)propyl]- carbamate	<u>303</u>		0.000000021
Phenylmethyl [(1S)-1- [[[(3R)-3-[[[(1S,2S)-1- (aminocarbonyl)-2-methyl- butyl]amino]carbonyl]-6,8- dichloro-2,3,4,9-tetra- hydro-1H-carbazol-3-yl]- amino]carbonyl]-3-phenyl- propyl]carbamate	<u>304</u>	0.000000018	0.000000038
Phenylmethyl [(1S)-1- [[[(3R)-3-[[[(1S,2S)-1- (aminocarbonyl)-2-methyl- butyl]amino]carbonyl]-6,8- dichloro-2,3,4,9-tetra- hydro-1H-carbazol-3-yl]- amino]carbonyl]-3-methyl- butyl]carbamate	<u>305</u>		0.000000056
Phenylmethyl [(1S)-1- [[[(3R)-3-[[[(1S)-1- (aminocarbonyl)-3-methyl- butyl]amino]carbonyl]-6,8- dichloro-2,3,4,9-tetra- hydro-1H-carbazol-3-yl]- amino]carbonyl]-3-methyl- butyl]carbamate	<u>306</u>		0.000000077

CLAIMS

1. A compound of the general formula (I)



(I)

in which

the radical R^1 is a hydrogen atom, a C_2-C_6 alkenyl or a C_1-C_6 alkyl radical and may optionally be substituted by an aryl, hetaryl radical or the group $-COOR^{11}$, where the aryl or hetaryl radical may be substituted by up to three substituents which are selected independently of one another from the group consisting of $-NO_2$, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$ and halogen atoms, and

the radical R^{11} is a hydrogen atom, a C_1-C_{12} alkyl, a C_1-C_{12} aralkyl, an aryl, hetaryl radical or the group $-COCH_3$ and may optionally be substituted by one substituent selected from the group consisting of $-CONH_2$, $-COCH_3$, $-COOCH_3$, $-SO_2CH_3$ and aryl radicals;

the radicals R^2 , R^3 , R^4 and R^5 are each independently of one another a hydrogen atom, a halogen atom, the group $-COOH$, $-CONH_2$, $-CF_3$, $-OCF_3$, $-NO_2$, $-CN$, a C_1-C_6 alkyl, a C_1-C_6 alkenyl, a C_1-C_6

alkoxy, a C₁-C₁₂ aralkyl, an aryl or hetaryl radical;

5 the radical R⁶ is the group -CONR⁸R⁹, -COOR⁸,
-CH₂NR⁸R⁹, -CH₂R⁸, -CH₂OR⁸ or a C₁-C₁₂ alkenyl radical
which is optionally substituted by the radicals R⁸
and R⁹,

where the radicals R⁸ and R⁹ are each independently
of one another a hydrogen atom, a C₁-C₁₂ alkyl, a
10 C₁-C₁₂ aralkyl, a C₁-C₁₂ hetaralkyl, an aryl or
hetaryl radical, each of which may be substituted
by one or more substituents selected from the
group consisting of -OH, -NH₂, -CONHR¹⁰, -COOR¹⁰,
-NH-C(=NH)-NH₂ and halogen atoms,

15 where the radical R¹⁰ is a hydrogen atom, a C₁-C₁₂
alkyl, a C₁-C₁₂ aralkyl, an aryl or hetaryl radical
and is optionally substituted by the group
-CON(R¹¹)₂,

or where the radicals R⁸ and R⁹ may together form a
20 cyclic structure which consists either exclusively
of carbon atoms or a combination of carbon atoms
and heteroatoms;

the radical R⁷ is a hydrogen atom, a C₁-C₁₂ alkyl, a
25 C₁-C₁₂ alkenyl, a C₁-C₁₂ aralkyl, an aryl or hetaryl
radical, the group -NR¹²R¹³, -NHCOR¹⁴, -NHCONHR¹⁴,
-NHCOOR¹⁴ or -NHSO₂R¹⁴ and may optionally be
substituted by one or more substituents selected
from the group consisting of -OH, -NH₂, -CONH₂,
30 -COOH and halogen atoms,

the radicals R¹² and R¹³ are each independently of
one another a hydrogen atom, a C₂-C₆ alkenyl or a
C₁-C₁₂ alkyl radical and may optionally be
substituted by one or more aryl or hetaryl
35 radicals which in turn may be substituted by up to
three substituents selected independently of one
another from the group consisting of -NO₂, -CH₃,
-CF₃, -OCH₃, -OCF₃ and halogen atoms,

and the radical R^{14} is a hydrogen atom, a C_1 - C_{12} alkyl, a C_1 - C_{12} alkenyl, a C_1 - C_{12} aralkyl, an aryl or hetaryl radical which may optionally be substituted by one or more substituents selected from the group consisting of $-NO_2$, $-CH_3$, $-OR^{11}$, $-CF_3$, $-OCF_3$, $-OH$, $-N(R^{11})_2$, $-OCOR^{11}$, $-COOH$, $-CONH_2$, $-NHCONHR^{11}$, $-NHCOOR^{11}$ and halogen atoms;

and the radicals R^a , R^b , R^c , R^d , R^e and R^f are each independently of one another a hydrogen atom, a halogen atom, the group $-COOH$, $-CONH_2$, $-CF_3$, $-OCF_3$, $-NO_2$, $-CN$, a C_1 - C_6 alkyl, C_1 - C_6 alkoxy, an aryl or hetaryl radical;

with the proviso that the compound of the general formula (I) is not selected from the group consisting of 3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-amino-6-benzyloxy-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, methyl 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylate, (-)-menthyl 3-acetamido-1,2,3,4-tetrahydrocarbazole-3-carboxylate or 3-tert-butoxycarbonylamino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid.

2. The compound as claimed in claim 1, where the radicals R^a , R^b , R^c , R^d , R^e and R^f are hydrogen atoms.

3. The compound as claimed in claim 1 or 2, where the radical R^1 is a hydrogen atom.

4. The compound as claimed in any of claims 1 to 3, where the radicals R^2 , R^3 , R^4 and/or R^5 are not hydrogen atoms.

5. The compound as claimed in claim 4, where the radicals R^2 , R^3 , R^4 and R^5 are independently of one another the group $-CH_3$, $-Cl$ or $-OCH_3$.
- 5 6. The compound as claimed in claim 5, where the compound is selected from the group consisting of phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-8-methyl-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, 10 phenylmethyl-[(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6-chloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, and 15 phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate.
- 20 7. The compound as claimed in any of claims 1 to 5, where the radical R^6 is a hydrophobic radical which includes alkyl, aryl and/or hetaryl structures and which carries a hydrogen bond donor-acceptor system at a distance of from two to four single 25 bonds, counting from the carbon atom substituted by the radicals R^6 and R^7 .
8. The compound as claimed in claim 7, where the radical R^6 is selected from the group consisting of 30 a phenylalanylamine residue, an isoleucylamine residue, a valyl-4-aminobenzamide residue, a valyl-N-methylamide residue, a methyloxymethyl-4-pyridyl radical, a carboxyl radical, an ethyl propenoate residue, a carbonylvalylamine residue, 35 a carbonylthreonylamine residue, a cyclic carboxamide residue, a 4-carboxamidophenyl-carboxamide residue, a methylaminomethyl-2-pyridyl radical, a carbonylvalinol residue and a methylvalinol residue.

9. The compound as claimed in claim 8, where the compound is selected from the group consisting of
- 5 phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]-carbonyl]-2-methylbutyl]carbamate,
- 10 phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]-carbonyl]-2-methylbutyl]carbamate,
- 15 phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-[[[4-(aminocarbonyl)phenyl]amino]carbonyl]-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate,
- 20 phenylmethyl [(1S,2S)-2-methyl-1-[[[(3R)-2,3,4,9-tetrahydro-3-[[[(1S)-2-methyl-1-(methylamino)-carbonyl]propyl]amino]carbonyl]-1H-carbazol-3-yl]amino]carbonyl]butyl]carbamate,
- 25 2,3,4,9-tetrahydro-3-(3-phenylpropyl)-O-(4-pyridinylmethyl)-1H-carbazole-3-methanol,
- 2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazole-3-carboxylic acid,
- 30 ethyl 3-[2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazol-3-yl]-2-propenoate,
- phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]-carbonyl]-2-methylbutyl]carbamate,
- 35 phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2R)-1-(aminocarbonyl)-2-hydroxypropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]-carbonyl]-2-methylbutyl]carbamate,
- phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(2S)-2-(aminocarbonyl)-1-pyrrolidinyl]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate,

phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(2S)-2-(aminocarbonyl)octahydro-1H-indol-1-yl]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate),

5 phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[4-(aminocarbonyl)phenyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate,

10 2,3,4,9-tetrahydro-3-(3-phenylpropyl)-N-(2-pyridinylmethyl)-1H-carbazole-3-methanamine,

phenylmethyl [(1S,2S)-1-[[[(3S)-3-[[[(1S)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate,

15 2,3,4,9-tetrahydro-N-[(1S)-1-(hydroxymethyl)-2-methylpropyl]-3-(3-phenylpropyl)-1H-carbazole-3-carboxamide and

(2S)-3-methyl-2-[[[2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1H-carbazol-3-yl]methyl]amino]-1-

20 butanol.

10. The compound as claimed in any of claims 1 to 5, 7 or 8, where the radical R⁷ is a hydrophobic radical including alkyl, aryl and/or hetaryl structures.

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11. The compound as claimed in claim 10, where the radical R⁷ is selected from the group consisting of a 2,3-biphenylpropionylamino radical, an indanoylamino radical, an indolylacetyl amino radical, a 2-naphthylacetyl amino radical, a 3-propionylamino radical, a phenylmethylcarboxamide residue which is substituted on the aromatic system, a phenylhexylamine residue and a phenylpropyl radical.

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12. The compound as claimed in claim 11, where the compound is selected from the group consisting of

- N*-[[(3*R*)-2,3,4,9-tetrahydro-3-[(1-oxo-2,3-diphenylpropyl)amino]-1*H*-carbazol-3-yl]carbonyl]-*L*-valyl-*L*-aspartamide,
- 5 (3*R*)-*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-3-[[(2,3-dihydro-1*H*-inden-1-yl)carbonyl]amino]-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxamide,
- (3*S*)-*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(1*H*-indol-3-ylacetyl)amino]-1*H*-carbazole-3-carboxamide,
- 10 (3*S*)-*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(2-naphthalinylacetyl)amino]-1*H*-carbazole-3-carboxamide,
- N*-[[(3*R*)-2,3,4,9-tetrahydro-3-[(2*S*,3*S*)-3-methyl-1-oxo-2-[(1-oxo-3-phenylpropyl)amino]pentyl]-amino]-1*H*-carbazol-3-yl]carbonyl]-*L*-valyl-*L*-
- 15 aspartamide,
- (3*R*)-*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[(4-methylphenyl)acetyl]amino]-1*H*-carbazole-3-carboxamide,
- 20 *N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[[(4-methoxyphenyl)acetyl]amino]-1*H*-carbazole-3-carboxamide,
- (3*R*)-*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-3-[[(3-bromophenyl)acetyl]amino]-2,3,4,9-tetrahydro-
- 25 1*H*-carbazole-3-carboxamide,
- (3*R*)-*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-3-[[(4-fluorophenyl)acetyl]amino]-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxamide,
- (3*R*)-*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-3-[[(4-chlorophenyl)acetyl]amino]-2,3,4,9-
- 30 tetrahydro-1*H*-carbazole-3-carboxamide,
- (3*R*)-*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-2,3,4,9-tetrahydro-3-[(6-phenylhexyl)amino]-1*H*-carbazole-3-carboxamide,
- 35 6,8-dichloro-2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1*H*-carbazole-3-carboxylic acid and ethyl 6,8-dichloro-2,3,4,9-tetrahydro-3-(3-phenylpropyl)-1*H*-carbazole-3-carboxylate.

13. The compound as claimed in any of claims 1 to 5,
7, 8, 10 or 11, where the compound is in the R
configuration at the carbon atom substituted by
the radicals R⁶ and R⁷ when the radicals R⁶ and R⁷
together form an alpha-amino carboxylic acid
structural element.
14. The compound as claimed in claim 1, where the
compound is selected from the group consisting of
phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-
(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-
6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-
yl]amino]carbonyl]-2-methylbutyl]carbamate,
phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-
(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-
2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]-
carbonyl]-2-methylbutyl]carbamate,
(2S)-1-[[[(3R)-3-[[[4-chlorophenyl]acetyl]amino]-
2,3,4,9-tetrahydro-8-methoxy-1H-carbazol-3-
yl]carbonyl]-2-pyrrolidinecarboxamide and
6,8-dichloro-2,3,4,9-tetrahydro-3-(3-phenyl-
propyl)-N-(2-pyridinylmethyl)-1H-carbazole-3-
methanamine.
15. A pharmaceutical composition comprising at least
one compound as claimed in any of claims 1 to 14.
16. The pharmaceutical composition as claimed in claim
15, where the compound is present in a unit dose
of from 1 µg to 100 mg per kg of a patient's body
weight.
17. The pharmaceutical composition as claimed in claim
15 or 16, where the compound is present in
combination with at least one further active
pharmaceutical ingredient and/or pharmaceutically
acceptable carrier in the composition.

18. A method for preparing a compound of formula (I) according to any of claims 1 to 14 which comprises:

a) producing a compound of formula (I) in which R^1 is hydrogen by condensing a suitably substituted cyclohexanone derivative with a suitably substituted phenylhydrazine derivative or a salt thereof;

b) producing a compound of formula (I) in which R^1 is hydrogen, by reacting a suitably substituted carboxylic acid and a suitably substituted amine component to give a suitably substituted carbamate group at either R^6 or R^7 ;

c) producing a compound of formula (I) in which R^1 is other than hydrogen by reacting an anion derived by deprotonating a compound of formula (I) in which R^1 is hydrogen with a compound of formula R^1-X , wherein R^1 has the same meaning as R^1 above, save that it does not represent hydrogen, and X represents a leaving group;

d) producing a compound of formula (I) by eliminating a corresponding compound of formula (I) from a solid phase wherein the compound is bound to a solid phase by a tether severing of which generates the group R^6 ; or

e) removing one or more protecting groups from a corresponding compound of formula (I) in protected form.

19. The compound as claimed in any of claims 1 to 14, for use in therapy.
20. The use of a compound as claimed in any of claims 1 to 14 for the manufacture of a medicament for the treatment of pathological states mediated by G protein-coupled receptors.
21. The use of a compound as defined in claim 1, but including the compounds specifically excluded in claim 1, for the manufacture of a medicament for inhibiting gonadotropin-releasing hormone.
22. The use as claimed in claim 20 or 21 wherein the medicament is used in male fertility control, in hormone therapy, treatment of female subfertility or infertility, female contraception and tumor control.
23. A compound as defined in claim 1, but including the compounds specifically excluded in claim 1, for use in male fertility control or for female contraception.
24. The compound as claimed in claim 1, where the compound is selected from the group consisting of phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]carbonyl]-6,8-difluoro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-8-methoxy-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-

- dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-3-methylbutyl]amino]carbonyl]-6,8-
- 5 dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-cyclohexylethyl]amino]carbonyl]-6,8-
- 10 dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2,2-dimethylpropyl]amino]carbonyl]-6,8-
- 15 dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-3-phenylpropyl]amino]carbonyl]-6,8-
- 20 dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-
- 25 dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-cyclohexylmethyl]carbamate, phenylmethyl [(1S,2S)-1-[[[(3R)-3-[[[(1S,2S)-1-(carboxy)-2-methylbutyl]amino]carbonyl]-6,8-
- 30 dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-2-methylbutyl]carbamate, phenylmethyl [(1S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-
- 35 dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-3-(4-hydroxyphenyl)propyl]carbamate, phenylmethyl [(1S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-

dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-3-phenylpropyl]carbamate, phenylmethyl [(1S)-1-[[[(3R)-3-[[[(1S,2S)-1-(aminocarbonyl)-2-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-3-methylbutyl]carbamate, phenylmethyl [(1S)-1-[[[(3R)-3-[[[(1S)-1-(aminocarbonyl)-3-methylbutyl]amino]carbonyl]-6,8-dichloro-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amino]carbonyl]-3-methylbutyl]carbamate.

25. A pharmaceutical composition comprising at least one compound as claimed in claim 24.

26. The pharmaceutical composition as claimed in claim 25, where the compound is present in a unit dose of from 1 μ g to 100 mg per kg of a patient's body weight.

27. The pharmaceutical composition as claimed in claim 25 or 26, where the compound is present in combination with at least one further active pharmaceutical ingredient and/or pharmaceutically acceptable carrier in the composition.

28. A method for preparing a compound of formula (I) according to claim 24 which comprises:

a) producing a compound of formula (I) in which R^1 is hydrogen by condensing a suitably substituted cyclohexanone derivative with a suitably substituted phenylhydrazine derivative or a salt thereof;

b) producing a compound of formula (I) in which R^1 is hydrogen, by reacting a suitably substituted

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carboxylic acid and a suitably substituted amine component to give a suitably substituted carbamate group at either R⁶ or R⁷;

5 c) producing a compound of formula (I) in which R¹ is other than hydrogen by reacting an anion derived by deprotonating a compound of formula (I) in which R¹ is hydrogen with a compound of formula R¹-X, wherein R¹ has the same meaning as R¹ above, save
10 that it does not represent hydrogen, and X represents a leaving group;

d) producing a compound of formula (I) by eliminating a corresponding compound of formula (I)
15 from a solid phase wherein the compound is bound to a solid phase by a tether severing of which generates the group R⁶; or

e) removing one or more protecting groups from a
20 corresponding compound of formula (I) in protected form.

29. The compound as claimed in claim 24, for use in therapy.

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30. The use of a compound as claimed in claim 24 for the manufacture of a medicament for the treatment of pathological states mediated by G protein-coupled receptors.

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31. The use of a compound as claimed in claim 24 for the manufacture of a medicament for inhibiting gonadotropin-releasing hormone.

32. The use as claimed in claim 30 or 31 wherein the medicament is used in male fertility control, in hormone therapy, treatment of female subfertility or infertility, female contraception and tumor control.
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