PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 239/94, A61K 31/505, A61P 9/00

A1

(11) International Publication Number: **WO 00/46214**

(43) International Publication Date: 10 August 2000 (10.08.00)

(21) International Application Number: PCT/EP00/00468

(22) International Filing Date: 22 January 2000 (22.01.00)

(30) Priority Data:
199 04 710.3 5 February 1999 (05.02.99) DE

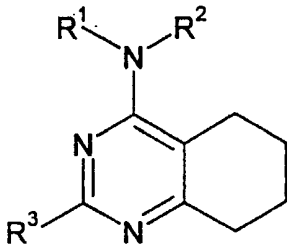
(71) Applicant: AVENTIS PHARMA DEUTSCHLAND GMBH [DE/DE]; Brüningstrasse 50, D–65929 Frankfurt am Main (DE).

(72) Inventors: SCHINDLER, Ursula; Robert–Stolz–Strasse 56, D–65812 Bad Soden (DE). SCHÖNAFINGER, Karl; Holunderweg 8, D–63755 Alzenau (DE). STROBEL, Hartmut; Erlenweg 22, D–65835 Liederbach (DE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SUBSTITUTED 4–AMINO–2–ARYLTETRAHYDROQUINAZOLINES, THEIR PREPARATION, THEIR USE AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM



(I)

(57) Abstract

The present invention relates to compounds of formula (I) in which R^1, R^2, and R^3 have the meanings indicated in the claims, which are valuable pharmaceutical active compounds for the therapy and prophylaxis of diseases, for example of cardiovascular disorders such as high blood pressure, angina pectoris, cardiac insufficiency, thromboses or atherosclerosis. The compounds of formula (I) have the ability to modulate the endogenous production of cyclic guanosine monophosphate (cGMP) and are generally suitable for the therapy and prophylaxis of disease states which are associated with a disturbed cGMP balance. The invention furthermore relates to processes for the preparation of compounds of formula (I), their use for the therapy and prophylaxis of the designated disease states and for the production of pharmaceuticals therefor, and pharmaceutical compositions which comprise a compound of formula (I).

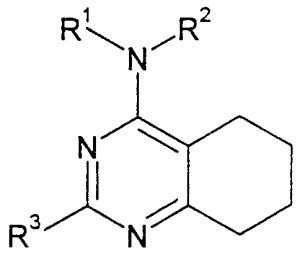
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Substituted 4-amino-2-aryltetrahydroquinazolines, their preparation, their use and pharmaceutical compositions comprising them

The present invention relates to compounds of the formula I



I

in which R^1, R^2 and R^3 have the meanings indicated below, which are valuable pharmaceutical active compounds for the therapy and prophylaxis of diseases, for example of cardiovascular disorders such as high blood pressure, angina pectoris, cardiac insufficiency, thromboses or atherosclerosis. The compounds of the formula I have the ability to modulate the endogenous production of cyclic guanosine monophosphate (cGMP) and are generally suitable for the therapy and prophylaxis of disease states which are associated with a disturbed cGMP balance. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use for the therapy and prophylaxis of the designated disease states and for the production of pharmaceuticals therefor, and pharmaceutical compositions which comprise a compound of the formula I.

cGMP is an important intracellular messenger which triggers a number of pharmacological effects by means of the modulation of cGMP-dependent protein kinases, phosphodiesterases and ion channels. Examples are smooth muscle relaxation, the inhibition of platelet activation and the inhibition of smooth muscle cell proliferation and leukocyte adhesion. cGMP is produced by particulate and soluble guanylate cyclases as a response to a number of extracellular and intracellular stimuli. In the case of the particulate guanylate cyclases, the stimulation essentially takes place by means of peptide signal substances, such as the atrial natriuretic peptide or the cerebral natriuretic peptide. The soluble guanylate cyclases (sGC),

which are cytosolic, heterodimeric heme proteins, however, are essentially regulated by a family of low molecular weight, enzymatically formed factors. The most important stimulant is nitrogen monoxide (NO) or a closely related species. The importance of other factors such as carbon monoxide or the hydroxyl radical is still largely unclear. The binding of NO to the heme with formation of a pentacoordinated heme-nitrosyl complex is discussed as an activation mechanism of activation by NO. The release associated therewith of the histidine which is bound to the iron in the basal state converts the enzyme into the activated conformation.

Active soluble guanylate cyclases are each composed of an α- and a β-subunit. Several subtypes of the subunits are described which differ from one another with respect to sequence, tissue-specific distribution and expression in various stages of development. The subtypes α_1 and β_1 are mainly expressed in the brain and lung, while β_2 is especially found in liver and kidney. The subtype α_2 was detected in human fetal brain. The subunits designated as α_3 and β_3 were isolated from human brain and are homologous to α_1 and β_1. More recent studies point to an α_{2i} subunit, which contains an insert in the catalytic domain. All subunits show great homology in the region of the catalytic domain. The enzymes probably contain one heme per heterodimer, which is bonded via β_1-Cys-78 and/or β_1-His-105 and is part of the regulatory center.

The formation of guanylate cyclase-activating factors can be decreased under pathological conditions, or increased degradation thereof can take place, for example as a result of the increased occurrence of free radicals. The decreased activation of the sGC resulting therefrom leads, via the attenuation of the respective cGMP-mediated cell response, to an increase in the blood pressure, to platelet activation or to increased cell proliferation or cell adhesion, for example. As a result, the formation of endothelial dysfunction, atherosclerosis, hypertension, stable or unstable angina pectoris, thromboses, myocardial infarcts, strokes or erectile dysfunction occurs. The pharmacological stimulation of the sGC offers a possibility for the normalization of cGMP production and thus allows the treatment and prevention of such diseases.

For the pharmacological stimulation of sGC, until now almost exclusively compounds were used whose action is based on an intermediate release of NO, for example organic nitrates. The disadvantage of this method of treatment lies in the development of tolerance and weakening of action and the higher dose which therefore becomes necessary.

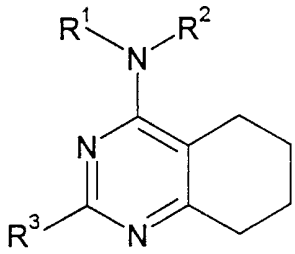
Various sGC stimulators which do not act via a release of NO were described by Vesely in a series of publications. However, the compounds which are mostly hormones, plant hormones, vitamins or, for example, natural substances such as lizard toxins, predominantly show only weak effects on cGMP formation in cell lysates (D. L. Vesely, Eur. J. Clin. Invest. 15 (1985) 258; D. L. Vesely, Biochem. Biophys. Res. Comm. 88 (1979) 1244). Stimulation of heme-free guanylate cyclase by protoporphyrin IX was detected by Ignarro et al. (Adv. Pharmacol. 26 (1994) 35). Pettibone et al. in (Eur. J. Pharmacol. 116 (1985) 307) described a hypotensive action for diphenyliodonium hexafluorophoshate and attributed this to a stimulation of sGC. Isoliquiritiginin, which shows a relaxant action on isolated rat aortas, likewise activates sGC according to Yu et al. (Brit. J. Pharmacol. 114 (1995) 1587). Ko et al. (Blood 84 (1994) 4226), Yu et al. (Biochem. J. 306 (1995) 787) and Wu et al. (Brit. J. Pharmacol. 116 (1995) 1973) detected an sGC stimulating activity of 1-benzyl-3-(5-hydroxymethyl-2-furyl)indazole and demonstrated an antiproliferative and platelet-inhibiting activity. An inhibitory action on platelet aggregation for various indazoles is described in EP-A-667 345. Heterocyclylmethyl-substituted and benzyl-substituted pyrazoles exhibiting sGC stimulating activity are furthermore described in WO-A-98/16 507 and WO-A-98/16 223.

Certain tetrahydroquinazolines are already known. For example, in DE-A-40 29 654, 2-phenyltetrahydroquinazolines having fungicidal activity are described which, in the 4-position, carry specific amino substituents which contain alkynyl groups. In US-A-3 346 452 and US-A-3 322 759 tetrahydroquinazolines are described which carry an aminoalkylamino group in the 4-position and which have analgesic activity. Specific bicyclic pyrimidines are described in WO-A-97/47 601 which act as

dopamine receptor antagonists and can be employed, for example, for the treatment of schizophrenia, and which carry a heterocyclylalkylamino substituent in which the heterocycle is bonded via a ring nitrogen atom. 2-Phenyl-cycloalkanopyrimidines are described in JP-A-07/228 573 which are serotonin receptor antagonists and are suitable as psychopharmaceuticals, and which carry a piperazino or homopiperazino substituent in the 4-position. 2-Phenylcycloalkanopyrimidines are described in EP-A-826 673 which act on benzodiazepine receptors and have, for example, an anxiolytic activity, and which carry specific amino substituents in the 4-position which contain aminocarbonyl groups.

Surprisingly, it has now been found that the fused pyrimidines of the formula I according to the invention bring about strong guanylate cyclase activation, on account of which they are suitable for the therapy and prophylaxis of diseases which are associated with a low cGMP level.

The present invention thus relates to compounds of the formula I



I

in which

R^1 and R^2, which are independent of one another and which can be identical or different, are hydrogen, or are (C_1-C_{10})-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxy, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl-S(O)$_m$-, (C_3-C_7)-cycloalkyl, phenyl, naphthyl and pyridyl, or are (C_3-C_9)-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, benzyl, hydroxy, amino, H-CO-O-, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-O-CO-O-, H-CO-NH-, (C_1-C_4)-

alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-, or are a residue of a 5-membered to 7-membered saturated heterocyclic ring which contains one or two identical or different hetero ring members from the group consisting of O, NR^{10} and $S(O)_m$ and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, hydroxy and aryl-(C_1-C_4)-alkyl-, but R^1 and R^2 cannot simultaneously be hydrogen,

or

the residue R^1R^2N- is a residue of a 5-membered to 7-membered saturated heterocyclic ring bonded via a ring nitrogen atom which in addition to the nitrogen atom bonded to the tetrahydroquinazoline ring can contain one further hetero ring member from the group consisting of O and $S(O)_m$ and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, phenyl, hydroxy, (C_1-C_4)-alkoxy, hydroxy-(C_1-C_4)-alkyl- and $R^{11}R^{12}N$-,

where phenyl groups, naphthyl groups, pyridyl groups and benzyl groups present in R^1, R^2 and R^1R^2N- can be unsubstituted or substituted in the aromatic ring by one or more identical or different substituents from the group consisting of halogen, (C_1-C_4)-alkyl, phenyl, CF_3, NO_2, OH, -O-(C_1-C_4)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_4)-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, -NH-(C_1-C_4)-alkyl, -N((C_1-C_4)-alkyl)$_2$, -NH-CHO, -NH-CO-(C_1-C_4)-alkyl, CN, -CO-NH_2, -CO-NH-(C_1-C_4)-alkyl, -CO-N((C_1-C_4)-alkyl)$_2$, -CO-OH, -CO-O-(C_1-C_4)-alkyl, -CHO and -CO-(C_1-C_4)-alkyl;

R^3 is aryl, but cannot be unsubstituted phenyl;

R^{10} is hydrogen, (C_1-C_4)-alkyl, aryl-(C_1-C_4)-alkyl-, hydroxy-(C_1-C_4)-alkyl-, hydroxycarbonyl-(C_1-C_4)-alkyl-, $((C_1-C_4)$-alkoxycarbonyl)-(C_1-C_4)-alkyl-, $R^{11}R^{12}N$-CO-(C_1-C_4)-alkyl-, R^{13}-SO_2- or aryl;

R^{11} and R^{12} are identical or different residues from the group consisting of hydrogen and (C_1-C_4)-alkyl;

R^{13} is (C_1-C_4)-alkyl, aryl or $R^{11}R^{12}N$-;

aryl is phenyl, naphthyl or heteroaryl which can all be substituted by one or more identical or different substituents from the group consisting of halogen, (C_1-C_4)-alkyl, phenyl, CF_3, NO_2, OH, -O-(C_1-C_4)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_4)-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, -NH-(C_1-C_4)-alkyl, -N$((C_1-C_4)$-alkyl$)_2$, -NH-CHO, -NH-CO-(C_1-C_4)-alkyl, CN, -CO-NH_2, -CO-NH-(C_1-C_4)-alkyl, -CO-N$((C_1-C_4)$-alkyl$)_2$, -CO-OH, -CO-O-(C_1-C_4)-alkyl, -CHO and -CO-(C_1-C_4)-alkyl;

heteroaryl is a residue of a monocyclic 5-membered or 6-membered aromatic heterocycle or of a bicyclic 8-membered to 10-membered aromatic heterocycle each of which containing one or more identical or different ring heteroatoms from the group consisting of N, O and S;

m is 0, 1 or 2;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically acceptable salts.

If residues, groups or substituents can occur several times in the compounds of the formula I they can all independently of one another have the indicated meanings and can in each case all be identical or different.

Alkyl residues can be straight-chain or branched. This also applies if they are contained in other groups, for example in alkoxy groups (-O-alkyl groups), alkoxycarbonyl groups or in amino groups, or if they are substituted. Examples of alkyl are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, the n-isomers of all these residues, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl,

neopentyl, 3,3-dimethylbutyl. The term alkyl here is expressly understood as including, in addition to saturated alkyl residues, also unsaturated alkyl residues which contain one or more double bonds, such as alkenyl residues. Examples of such alkyl residues are vinyl, 1-propenyl, 2-propenyl (allyl), 2-butenyl, 2-methyl-2-propenyl or 3-methyl-2-butenyl. Alkyl residues can be unsubstituted or substituted as indicated. If alkyl residues are substituted by one or more substituents they are preferably substituted by one, two or three, in particular by one or two, identical or different substituents. Substituents can be situated in all suitable positions of an alkyl residue.

Cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or cyclononyl, which can all also be substituted as indicated, for example by one or more identical or different substituents such as (C_1-C_4)-alkyl including methyl and isopropyl, and/or hydroxy, and/or acyloxy including acetyloxy, propionyloxy, butyryloxy, isobutyryloxy and pivaloyloxy, and/or amino, and/or substituted amino groups including the abovementioned acylamino groups like acetylamino and optionally substituted benzoylamino and sulfonylamino groups like methanesulfonylamino and optionally substituted benzenesulfonylamino. If cycloalkyl residues are substituted by one or more substituents, they are preferably substituted by one, two, three or four, in particular by one or two, identical or different substituents. Examples of such substituted cycloalkyl residues are 4-methylcyclohexyl, 4-tert-butylcyclohexyl, 4-hydroxycyclohexyl, 4-acetyloxycyclohexyl, 4-aminocyclohexyl, 4-acetylaminocyclohexyl, 4-ethoxycarbonylaminocyclohexyl, 3-methylcyclopentyl, 3-hydroxycyclopentyl, 3-aminocyclopentyl or 2,3-dimethylcyclopentyl. Substituents can be situated in all suitable positions of a cycloalkyl residue.

Carbocyclic aryl residues such as phenyl residues and naphthyl residues and heterocyclic aryl residues (= heteroaryl residues) can, if not stated otherwise, be unsubstituted or carry one or more, for example one, two, three or four, identical or different substituents which can be situated in all suitable positions. If not stated otherwise, for example the substituents indicated in the definition of the group aryl

can occur as substituents in these residues. (C_1-C_2)-Alkylenedioxy can, for example, be methylenedioxy or ethylenedioxy. If nitro groups are present as substituents in a compound of the formula I, altogether only up to two nitro groups can be present in the molecule. If an aryl residue such as, for example, a phenyl residue carries a further phenyl residue as substituent, the latter phenyl residue can also be unsubstituted or substituted by one or more, for example one, two, three or four, identical or different substituents, in particular by substituents from the group consisting of (C_1-C_4)-alkyl, halogen, hydroxy, (C_1-C_4)-alkoxy, trifluoromethyl, cyano, hydroxycarbonyl, ((C_1-C_4)-alkoxy)carbonyl, aminocarbonyl, nitro, amino, (C_1-C_4)-alkylamino, di-((C_1-C_4)-alkyl)amino and ((C_1-C_4)-alkyl)carbonylamino.

In monosubstituted phenyl residues the substituent can be situated in the 2-position, the 3-position or the 4-position. In disubstituted phenyl residues the substituents can be situated in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl residues the substituents can be situated in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. Naphthyl can be 1-naphthyl or 2-naphthyl. In monosubstituted 1-naphthyl residues the substituent can be situated in the 2-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position, in monosubstituted 2-naphthyl residues in the 1-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position. In polysubstituted naphthyl residues, for example di- or trisubstituted naphthyl residues, the substituents can also be situated in all suitable positions.

If not stated otherwise, heteroaryl residues, residues of saturated heterocyclic rings and residues of rings which are formed by two groups bonded to a nitrogen atom together with this nitrogen atom are preferably derived from heterocycles which contain one, two, three or four identical or different ring heteroatoms, more preferably from heterocycles which contain one or two or three, particular preferably one or two, identical or different ring heteroatoms. If not stated otherwise, the heterocycles can be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. Preferably,

they are monocyclic or bicyclic, in particular monocyclic. The individual rings preferably contain 5, 6 or 7 ring members. Examples of monocyclic and bicyclic heterocyclic systems from which residues occurring in the compounds of the formula I can be derived are pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,3-dioxole, 1,3-oxazole, 1,2-oxazole, 1,3-thiazole, 1,2-thiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxin, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, 1,3-oxazepine, 1,3-thiazepine, indole, benzothiophene, benzofuran, benzothiazole, benzimidazole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, thienothiophenes, 1,8-naphthyridine and other naphthyridines, pteridine, or phenothiazine, all in each case in saturated form (perhydro form) or in partially unsaturated form (for example dihydro form or tetrahydro form) or in maximally unsaturated or aromatic form, if the forms concerned are known and stable. Thus, the heterocycles which are suitable also include, for example, the saturated heterocycles pyrrolidine, piperidine, perhydroazepine (= hexamethyleneimine), piperazine, morpholine, 1,3-thiazolidine and thiomorpholine which - if this is in accord with the respective definition - are examples of residues of saturated heterocyclic rings and of residues of rings which are formed by two groups bonded to a nitrogen atom together with this nitrogen atom. The degree of saturation of heterocyclic groups is indicated in the individual definitions. Unsaturated heterocycles can, for example, contain one, two or three double bonds in a ring, and 5-membered rings and 6-membered rings in monocyclic and polycyclic heterocycles can in particular also be aromatic.

Heterocyclic residues can be bonded via any suitable ring carbon atom. Nitrogen heterocycles, for example pyrrole, imidazole, pyrrolidine, piperidine, hexamethyleneimine, 1,3-thiazolidine, morpholine, thiomorpholine, piperazine etc., can also be bonded via any suitable ring nitrogen atom, in particular if the nitrogen heterocycle is bonded to a carbon atom. For example, thienyl can be present as 2-thienyl or 3-thienyl, furyl as 2-furyl or 3-furyl, piperidyl as 1-piperidyl (= piperidino), 2-piperidyl, 3-piperidyl or 4-piperidyl, (thio)morpholinyl as 2-(thio)morpholinyl,

3-(thio)morpholinyl or 4-(thio)morpholinyl (= (thio)morpholino). A residue which is derived from 1,3-thiazole can be bonded via the 2-position, the 3-position, the 4-position or the 5-position, a residue which is derived from imidazole can be bonded via the 1-position, the 2-position, the 4-position or the 5-position. Pyridyl can be 2-pyridyl, 3-pyridyl or 4-pyridyl.

If not stated otherwise, the heterocyclic groups can be unsubstituted or can carry one or more, for example one, two, three or four, in particular one or two, identical or different substituents. The substituents in heterocycles can be situated in any desired suitable positions, for example in a 2-thienyl residue or 2-furyl residue in the 3-position and/or in the 4-position and/or in the 5-position, in a 3-thienyl residue or 3-furyl residue in the 2-position and/or in the 4-position and/or in the 5-position, in a 2-pyridyl residue in the 3-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 3-pyridyl residue in the 2-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 4-pyridyl residue in the 2-position and/or in the 3-position and/or in the 5-position and/or in the 6-position. If not stated otherwise, the substituents which can occur in heterocycles can be, for example, the substituents indicated in the definition of the group aryl, and in the case of saturated or partially unsaturated heterocycles further substituents can also be the oxo group (=O) and the thioxo group (=S). Two substituents on a heterocycle and just so substituents on a carbocycle can also form a ring, i. e. further rings can be fused to a ring system such that cyclopenta-fused, cyclohexa-fused or benzo-fused rings, for example, can be present. If not stated otherwise, possible substituents on a suitable ring nitrogen atom of a heterocycle are, for example, unsubstituted and substituted $(C_1\text{-}C_4)$-alkyl, aryl, acyl such as -CO-$(C_1\text{-}C_4)$-alkyl or -CO-aryl, or sulfonyl groups such as -SO_2-$(C_1\text{-}C_4)$-alkyl or -SO_2-aryl. Suitable sulfur heterocycles can also be present as S-oxides or S,S-dioxides, i.e., instead of a sulfur atom the group S(=O) or the group $S(=O)_2$ can be present as a ring member. Suitable nitrogen atoms in the compounds of the formula I can also be present as N-oxides or as quaternary salts with an anion derived from a physiologically acceptable acid as counterion. Pyridyl groups can be present, for example, as pyridine N-oxides.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

The present invention includes all stereoisomeric forms of the compounds of the formula I. Asymmetric centers present in the compounds of the formula I can all independently of one another have S configuration or R configuration. The invention includes all possible enantiomers and diastereomers, as well as mixtures of two or more stereoisomeric forms, for examples mixtures of enantiomers and/or diastereomers, in all ratios. The invention thus relates to enantiomers in enantiomerically pure form, both as dextrorotatory and as levorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the presence of cis/trans isomerism, for example on cycloalkyl groups, the invention relates both to the cis form and the trans form and mixtures of these forms in all ratios. Individual stereoisomers can be prepared, if desired, by resolution of a mixture according to customary methods, for example by chromatography or crystallization, by use of stereochemically homogeneous starting substances in the synthesis or by stereoselective synthesis. If appropriate, a derivatization can be carried out before separation of stereoisomers. The separation of a stereoisomer mixture can be carried out at the stage of the compounds of the formula I or at the stage of an intermediate in the course of the synthesis. If mobile hydrogen atoms are present, the present invention also includes all tautomeric forms of the compounds of the formula I.

The present invention also relates to the physiologically acceptable or toxicologically acceptable salts, in particular the pharmaceutically utilizable salts, of the compounds of the formula I which contain one or more acidic groups and/or basic groups. Thus in the compounds of the formula I which contain acidic groups, these groups can be present, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts and can be used according to the invention. Examples of such salts are sodium salts, potassium salts, calcium salts, magnesium salts, salts with physiologically acceptable quaternary ammonium ions or acid addition salts with ammonia or organic amines, for example with ethylamine, ethanolamine, triethanolamine or amino acids.

Compounds of the formula I which contain one or more basic, i.e. protonatable, groups can be present in the form of their acid addition salts with physiologically acceptable inorganic or organic acids and can be used according to the invention, for example as salts with hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfamic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid etc. If the compounds of the formula I simultaneously contain acidic and basic groups in the molecule, in addition to the salt forms outlined before the invention also includes internal salts or betaines (zwitterions). Salts can be obtained from the compounds of the formula I by customary processes known to the person skilled in the art, for example by combination with an organic or inorganic acid or base in a solvent or diluent or alternatively from other salts by anion exchange or cation exchange. The present invention also includes all salts of the compounds of the formula I which, because of low physiological tolerability, are not directly suitable for use in pharmaceuticals, but are suitable, for example, as intermediates for chemical reactions or for the preparation of physiologically acceptable salts.

The present invention furthermore includes all solvates and addition compounds of compounds of the formula I, in particular physiologically acceptable ones, for example hydrates or adducts with alcohols, and also derivatives of the compounds of the formula I such as, for example, esters, and prodrugs and active metabolites.

Preferably, one of the residues R^1 and R^2 is $(C_1\text{-}C_8)$-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxy, $(C_1\text{-}C_4)$-alkoxy, $(C_1\text{-}C_4)$-alkyl-$S(O)_m$-, $(C_3\text{-}C_7)$-cycloalkyl, phenyl and naphthyl, or is $(C_3\text{-}C_9)$-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of $(C_1\text{-}C_4)$-alkyl, benzyl, hydroxy, amino, H-CO-O-, $(C_1\text{-}C_4)$-alkyl-CO-O-, $(C_1\text{-}C_4)$-alkyl-O-CO-O-, H-CO-NH-, $(C_1$-

C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-, where phenyl groups, naphthyl groups and benzyl groups present in the residues R^1 and R^2 can be unsubstituted or substituted in the aromatic ring. Preferably, the other of the residues R^1 and R^2 is hydrogen, or is (C_1-C_8)-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxy, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl-$S(O)_m$-, (C_3-C_7)-cycloalkyl, phenyl and naphthyl, or is (C_3-C_9)-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, benzyl, hydroxy, amino, H-CO-O-, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-O-CO-O-, H-CO-NH-, (C_1-C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-, where phenyl groups, naphthyl groups and benzyl groups present in the residues R^1 and R^2 can be unsubstituted or substituted in the aromatic ring.

It is particularly preferred if one of the residues R^1 and R^2 is (C_1-C_8)-alkyl or is (C_3-C_9)-cycloalkyl and the other of the residues R^1 and R^2 is hydrogen, or if both residues R^1 and R^2 are identical or different (C_1-C_8)-alkyl groups, where all alkyl groups and cycloalkyl groups can be unsubstituted or substituted as indicated. It is especially preferred if one of the residues R^1 and R^2 is (C_3-C_9)-cycloalkyl which is unsubstituted or substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, benzyl, hydroxy, amino, H-CO-O-, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-O-CO-O-, H-CO-NH-, (C_1-C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-, where phenyl groups and benzyl groups present in the residues R^1 and R^2 can be unsubstituted or substituted in the aromatic ring, and the other of the residues R^1 and R^2 is hydrogen.

If one of the residues R^1 and R^2 is (C_3-C_9)-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, benzyl, hydroxy, amino, H-CO-O-, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-O-CO-O-, H-CO-NH-, (C_1-C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-

alkyl-SO_2-NH- and phenyl-SO_2-NH-, or is a residue of a 5-membered to 7-membered saturated heterocyclic ring which contains one or two identical or different hetero ring members from the group consisting of O, NR^{10} and $S(O)_m$ and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, hydroxy and aryl-(C_1-C_4)-alkyl-, then the other of the residues R^1 and R^2 is preferably hydrogen.

An alkyl residue representing R^1 or R^2 is preferably an unsubstituted or substituted (C_1-C_4)-alkyl residue. A (C_3-C_9)-cycloalkyl residue representing R^1 or R^2 is preferably an unsubstituted or substituted (C_3-C_7)-cycloalkyl residue from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, particularly preferably an unsubstituted or substituted (C_5-C_6)-cycloalkyl residue from the group consisting of cyclopentyl and cyclohexyl. If a cycloalkyl residue representing R^1 or R^2 is substituted it is preferably substituted by one or more substituents from the group consisting of (C_1-C_4)-alkyl, hydroxy, amino, H-CO-O-, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-O-CO-O-, H-CO-NH-, (C_1-C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-, where phenyl groups present in the residues R^1 and R^2 can be unsubstituted or substituted. Particularly preferably, a substituted cycloalkyl residue representing R^1 or R^2 is substituted by one or more substituents from the group consisting of (C_1-C_4)-alkyl, hydroxy, amino, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-, where phenyl groups present in the residues R^1 and R^2 can be unsubstituted or substituted. Especially preferably, a cycloalkyl residue representing R^1 or R^2 is substituted by one or more (C_1-C_4)-alkyl residues or by a hydroxy group or by an amino group, in particular by a hydroxy group.

A residue of a 5-membered to 7-membered saturated heterocyclic ring representing R^1 or R^2 preferably contains one hetero ring member from the group consisting of O, NR^{10} and $S(O)_m$, particularly preferably a group NR^{10}, as a hetero ring member.

Preferably, a heterocyclic ring of this type is bonded via a ring carbon atom which is not directly adjacent to a hetero ring member. Examples of residues of heterocyclic rings of this type are optionally substituted pyrrolidinyl, for example 3-pyrrolidinyl, optionally substituted piperidyl, for example 3-piperidyl or 4-piperidyl, tetrahydrofuryl, for example 3-tetrahydrofuryl, tetrahydrothienyl and its S-oxide and S,S-dioxide, for example 3-tetrahydrothienyl, or tetrahydro(thio)pyranyl.

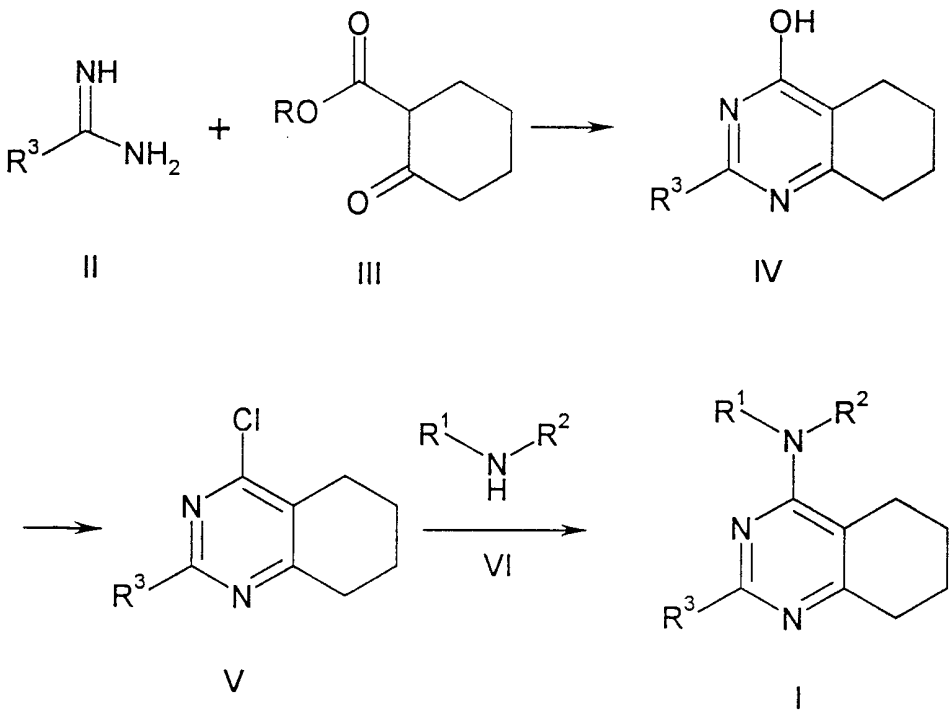
In addition to the abovementioned preferred meanings of R^1 and R^2, it is furthermore preferred if the residue R^1R^2N- is a residue of a 5-membered, 6-membered or 7-membered saturated heterocyclic ring which is bonded via a ring nitrogen atom and which, in addition to the nitrogen atom bonded to the tetrahydroquinazoline ring, can contain one oxygen atom or one group $S(O)_m$ as a further hetero ring member and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, hydroxy, (C_1-C_4)-alkoxy, hydroxy-(C_1-C_4)-alkyl- and $R^{11}R^{12}N$-. A residue of a heterocyclic ring representing R^1R^2N- is preferably derived from a 5-membered or 6-membered saturated heterocyclic ring, particularly preferably from piperidine, morpholine or thiomorpholine (and its S-oxide and S,S-dioxide) which can all be substituted as indicated, very particularly preferably from unsubstituted piperidine, morpholine or thiomorpholine (and its S-oxide and S,S-dioxide).

The aryl group representing R^3 preferably is substituted phenyl which is substituted as indicated above for substituted aryl, particularly preferably phenyl which is substituted by one or two identical or different substituents from those indicated above for aryl. Especially preferably, R^3 is phenyl which is substituted by one or two substituents from the group consisting of halogen, -O-(C_1-C_4)-alkyl and (C_1-C_4)-alkyl, in particular from the group consisting of halogen and (C_1-C_4)-alkyl, moreover preferably phenyl which is substituted by substituents from the group consisting of fluorine, chlorine and methyl. The substituent in a monosubstituted phenyl group representing R^3 is preferably in the meta-position or para-position.

Aryl is preferably phenyl or 5-membered or 6-membered monocyclic heteroaryl having one or two, in particular one, ring heteroatom from the group consisting of N, O and S which can be substituted as indicated above, particularly preferably unsubstituted or substituted phenyl or unsubstituted pyridyl, thienyl or furyl, very particularly preferably unsubstituted or substituted phenyl or unsubstituted pyridyl.

Preferred compounds of the formula I are those in which one or more of the residues contained therein have preferred meanings. The present invention relates to all combinations of preferred definitions of residues and substituents and/or of one or more specific meanings of residues and substituents which are indicated in their definitions or in the additional explanations on residues, substituents and groups. Also with respect to all preferred compounds of the formula I the present invention comprises all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically acceptable salts.

The present invention also relates to processes for the preparation of the compounds of the formula I which are explained below and by which the compounds according to the invention are obtainable. The compounds of the formula I can be prepared by first reacting an amidine of the formula II in an manner known per se with a 2-oxocyclohexanecarboxylic acid ester of the formula III to give a 4-hydroxy-tetrahydroquinazoline of the formula IV. The residue R in the formula III is, for example, (C_1-C_4)-alkyl such as methyl or ethyl. The residues R^1, R^2 and R^3 in the formulae II, IV, V and VI have the meanings indicated above for the formula I. The hydroxytetrahydroquinazoline of the formula IV is then activated, for example by conversion into a 2-aryl-4-halo-5,6,7,8-tetrahydroquinazoline. For example, the compounds of the formula IV can be converted into the 4-chlorotetrahydro-quinazolines of the formula V by reaction with a phosphorus halide such as phosphorus oxychloride. By reaction of a compound of the formula V (or of another reactive derivative of the hydroxytetrahydroquinazoline) with the desired amine of the formula VI the compound of the formula I according to the invention is then obtained



with replacement of the chlorine by the amino group. Suitable solvents for this replacement reaction are, for example, water, alcohols such as methanol, ethanol or isopropanol, ethers such as tetrahydrofuran or dioxane, amides such as dimethylformamide (DMF) or N-methylpyrrolidone (NMP), or hydrocarbons or halogenated hydrocarbons such as benzene, toluene, xylene, chlorobenzene or dichlorobenzene. The above reactions can be carried out in a wide temperature range. Reaction temperatures from about 20°C to about 150°C are preferred. The reactions can be accelerated by addition of suitable bases such as, for example, sodium bicarbonate, sodium carbonate, potassium carbonate, alkali metal alkoxides such as sodium alkoxides or potassium alkoxides, or amines such as triethylamine or pyridine, in the first and in the last step additionally also by excess amidine or amine, respectively. Instead of the free amidines of the formula II, the corresponding amidinium salts like, for example, the amidinium hydrochlorides can also be employed. In this case, it is particularly convenient to carry out the first step with addition of a base. Likewise, the amines of the formula VI employed in the last step can also be employed in the form of salts which are converted into the free amines in situ or in a separate step using a base. The intermediates of the formulae IV and V

and the final compounds of the formula I can be separated from the respective reaction mixture by customary processes such as extraction, crystallization, sublimation, chromatography or distillation and, if desired, purified, but depending on the circumstances of the individual case the intermediates can also be reacted further without intermediary isolation. Moreover, functional groups in the compounds obtained can be subject to conversion reactions. For example, thioether groups can be converted into sulfones or sulfoxides by oxidation with a peroxy compound such as 3-chloroperbenzoic acid or monoperoxyphthalic acid or hydrogen peroxide, or carboxylic acid ester groups can be hydrolyzed to the carboxylic acids or converted into amides, or acylations can be carried out.

All reactions for the synthesis of the compounds of the formula I are well-known per se to the person skilled in the art and can be carried out under standard conditions according to or analogously to literature procedures such as are described, for example, in Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Thieme-Verlag, Stuttgart, or Organic Reactions, John Wiley & Sons, New York. Depending on the circumstances of the individual case, it may also be advantageous or necessary for the avoidance of side reactions during the synthesis of the compounds of the formula I to temporarily block certain functional groups by the introduction of protective groups and then later to liberate them again or at first to employ functional groups in the form of precursor groups from which the desired functional groups are then produced in later steps. Such synthesis strategies and the protective groups or precursors suitable for the individual case are known to the person skilled in the art. The starting amidines of the formula II or their salts, the oxoesters of the formula III and the amines of the formula VI are commercially available or can be prepared by or analogously to well-known processes.

The compounds of the formula I according to the invention bring about an increase in the cGMP concentration by means of the activation of soluble guanylate cyclase (sGC) and are therefore valuable agents for the therapy and prophylaxis of diseases which are associated with a low or reduced cGMP level or are caused by such a level, or for whose therapy or prophylaxis an increase in the cGMP level that is

present is desired. The activation of sGC by the compounds of the formula I can be investigated, for example, in the activity assay described below. Preferred substances of the formula I are those which exhibit in this assay an at least three-fold stimulation of the sGC activity.

Diseases and pathological conditions which are associated with a low cGMP level or in which an increase in the cGMP level is desirable and for whose therapy and prophylaxis compounds of the formula I can be employed are, for example, cardiovascular disorders such as endothelial dysfunction, diastolic dysfunction, atherosclerosis, hypertension, stable and unstable angina pectoris, thromboses, restenoses, myocardial infarcts, strokes, cardiac insufficiency or pulmonary hypertension, or, for example, erectile dysfunction, bronchial asthma, chronic renal insufficiency and diabetes. Compounds of the formula I can moreover be employed in the therapy of liver cirrhosis and for improving restricted learning capacity or memory power.

The compounds of the formula I and their physiologically acceptable salts can thus be used in animals, preferably in mammals, and in particular in humans, as pharmaceuticals on their own, in mixtures with one another or in the form of pharmaceutical compositions. The present invention therefore also relates to the compounds of the formula I and their physiologically acceptable salts for use as pharmaceuticals or medicaments, their use for the normalization of a disturbed cGMP balance and in particular their use in the therapy and prophylaxis of the abovementioned diseases and conditions, and their use for the production of pharmaceutical compositions therefor. The present invention furthermore relates to pharmaceutical compositions or pharmaceutical preparations which contain an efficacious dose of one or more compounds of the formula I and/or of its/their physiologically acceptable salts as an active constituent and a physiologically acceptable carrier.

The pharmaceuticals according to the invention can be administered orally, for example in the form of pills, tablets, film-coated tablets, coated tablets, granules, hard

and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories. The administration can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously in the form of injection solutions or infusion solutions. Further possible administration forms are, for example, percutaneous or topical application, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or administration by inhalation in the form of nasal sprays or aerosol mixtures or administration in the form of, for example, microcapsules, implants or rods. The preferred administration form depends, for example, on the disease to be treated and its severity.

The pharmaceutical compositions normally contain approximately 0.2 to 1000 mg, preferably 0.2 to 500 mg, in particular 1 to 200 mg, of active compound of the formula I and/or its physiologically acceptable salts and a physiologically acceptable carrier, i. e. one or more physiologically acceptable and pharmaceutically suitable vehicles and/or additives. The pharmaceutical compositions can be produced in a manner known per se. For this, one or more compounds of the formula I and/or their physiologically acceptable salts are brought, together with one or more solid or liquid pharmaceutical vehicles and/or additives and, if desired, with one or more other pharmaceutical active compounds having therapeutic or prophylactic action, into a suitable administration form and dosage form which can then be used as a pharmaceutical in human or veterinary medicine. The pharmaceutical compositions normally contain 0.5 to 90% by weight of the compounds of the formula I and/or their physiologically acceptable salts.

For the production, for example, of pills, tablets, coated tablets and hard gelatin capsules, lactose, starch, for example corn starch, or starch derivatives, talc, stearic acid or its salts, etc. can be used. Vehicles for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils etc. Suitable vehicles for the preparation of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, physiological saline solution, alcohols such as ethanol, glycerol, polyols, sucrose, invert sugar, glucose, mannitol,

vegetable oils etc. The compounds of the formula I and their physiologically acceptable salts can also be lyophilized and the lyophilizates obtained be used, for example, for the production of injection solutions or infusion solutions. Suitable vehicles for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid.

In addition to the active compounds and vehicles, the pharmaceutical compositions can additionally contain customary additives or auxiliaries, for example fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, sweetening agents, colorants, flavorings, aromatizers, thickening agents, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents and/or antioxidants.

The dose of the active compound of the formula I and/or its physiologically acceptable salt to be administered depends on the individual case and is to be suited to the individual conditions as customary for an optimal action. Thus it depends, for example, on the nature and severity of the disease to be treated, on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the potency and duration of action of the specific compound employed, on whether the therapy is acute or chronic or prophylaxis is carried out, or on whether further active compounds are administered in addition to compounds of the formula I. In general, a daily dose of approximately 0.01 to 100 mg/kg, preferably 0.1 to 10 mg/kg, in particular 0.3 to 5 mg/kg (in each case mg per kg of body weight) is appropriate in the case of administration to an adult of about 75 kg in weight to achieve the desired action. The daily dose can be administered in a single dose or, in particular in the case of administration of relatively large amounts, be divided into a number of individual doses, for example two, three or four doses. Depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the formula I activate soluble guanylate cyclase. On account of this property, apart from as pharmaceutical active compounds in human medicine and veterinary medicine, they can also be used as a scientific tool or as an aid for biochemical investigations in which an effect on guanylate cyclase of this type is intended, and also for diagnostic purposes, for example in the in vitro diagnosis of cell or tissue samples. In addition, the compounds of the formula I and their salts, as already mentioned above, can serve as intermediates for the preparation of further pharmaceutical active compounds.

The following examples illustrate the invention without restricting it.

Examples

Example 1

2-(4-Chlorophenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline

7.5 g of ethyl 2-oxocyclohexane-1-carboxylate and 9.6 g of 4-chlorobenzamidine hydrochloride were introduced into 50 ml of methanol. 5.6 g of potassium tert-butylate were added with stirring. The reaction mixture was stirred under reflux for 4 hours and then poured onto ice water. The crystalline product was filtered off with suction, washed with water and recrystallized from dimethylformamide. Yield: 8.8 g. M.p.: >300°C.

The intermediates of Examples 2 to 12 were prepared analogously to Example 1.

Example 2

2-(3-Chlorophenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 239°C.

Example 3

2-(4-Methoxyphenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 245°C.

Example 4

2-(3,5-Dichlorophenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 265°C.

Example 5

2-(2,4-Dichlorophenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 232°C.

Example 6

2-(3,4-Dichlorophenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 271°C.

Example 7

2-(2-Chlorophenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 181°C.

Example 8

2-(4-Aminocarbonylphenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 270°C.

Example 9

2-(4-Methylphenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 263°C.

Example 10

2-(3,4-Dimethoxyphenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 225°C.

Example 11

2-(3-Bromophenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 246°C.

Example 12

2-(3,5-Difluorophenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline; m.p.: 250°C.

Example 13

2-(4-Chlorophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline

8.0 g of 2-(4-chlorophenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline were heated to 100°C in 10 ml of phosphorus oxychloride. After 3 hours, the cooled solution was carefully poured onto ice water. The crystalline product was filtered off with suction,

washed well with water and dried in vacuo at room temperature. Yield: 6.2 g. M.p.: 121°C.

The intermediates of Examples 14 to 24 were prepared analogously to Example 13.

Example 14

2-(3-Chlorophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline; m.p.: 121°C.

Example 15

2-(4-Methoxyphenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline; m.p.: 112°C.

Example 16

2-(3,5-Dichlorophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline; m.p.: 183°C.

Example 17

2-(2,4-Dichlorophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline; m.p.: 111°C.

Example 18

2-(3,4-Dichlorophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline; m.p.: 138°C.

Example 19

2-(2-Chlorophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline; m.p.: 76°C.

Example 20

2-(4-Cyanophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline

The compound was obtained from 2-(4-aminocarbonylphenyl)-4-hydroxy-5,6,7,8-tetrahydroquinazoline (Example 8) by the procedure of Example 13. M.p.: 190°C.

Example 21

2-(4-Methylphenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline; m.p.: 117°C.

Example 22

2-(3,4-Dimethoxyphenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline; m.p.: 146°C.

Example 23

2-(3-Bromophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline; m.p.: 93°C.

Example 24

2-(3,5-Difluorophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline; m.p.: 130°C.

Example 25

2-(4-Chlorophenyl)-4-cyclopentylamino-5,6,7,8,7-tetrahydroquinazoline

0.25 g of 2-(4-chlorophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline, 0.4 g of cyclopentylamine and 1 ml of N-methylpyrrolidone were heated in an oil bath to 130°C. After 5 hours the mixture was diluted with 20 ml of water and stirred at room temperature. The precipitated product was filtered off with suction, washed with water and dried in vacuo at 40°C. Yield: 0.23 g. M.p.: 128°C.

Example 26

2-(4-Chlorophenyl)-4-(trans-4-hydroxycyclohexylamino)-5,6,7,8-tetrahydroquinazoline methanesulfonic acid salt

0.15 g of 2-(4-chlorophenyl)-4-chloro-5,6,7,8-tetrahydroquinazoline, 0.39 g of trans-4-aminocyclohexanol hydrochloride, 0.18 g of potassium tert-butylate and 1.5 ml of N-methylpyrrolidone were heated in an oil bath at 130°C for 2 hours. 15 ml of water were added to the cooled solution and the precipitated product was filtered off with suction. The dried solid was taken up in 8 ml of ethyl acetate and 2 ml of isopropanol and treated with methanesulfonic acid. The precipitated product was filtered off with suction, washed with ethyl acetate and dried in vacuo at 40°C. Yield: 0.13 g. M.p.: 224°C.

The compounds of the formula I of Examples 27 to 114 were prepared analogously to Examples 25 and 26.

Example	R^3 (in formula I)	R^1R^2N- (in formula I)	M.p. (°C)
27	4-chlorophenyl	trans-4-hydroxycyclohexylamino	219
28	4-chlorophenyl	2-hydroxyethylamino	186
29	4-chlorophenyl	butylamino	107
30	4-chlorophenyl	2-(3-methoxyphenyl)ethylamino	oil
31	4-chlorophenyl	dipropylamino	92
32	4-chlorophenyl	cis-2,6-dimethylmorpholino	141
33	4-chlorophenyl	5-hydroxy-1,5-dimethylhexylamino	oil
34	4-chlorophenyl	4-hydroxybutylamino	138
35	4-chlorophenyl	4-hydroxypiperidino	149
36	4-chlorophenyl	cis/trans-4-hydroxycyclohexylamino	185
37	4-chlorophenyl	4-acetyloxycyclohexylamino	195
38	4-chlorophenyl	trans-4-aminocyclohexylamino	251
39	4-chlorophenyl	trans-4-acetylaminocyclohexylamino	301 (dec.)
40	4-chlorophenyl	trans-4-methanesulfonylamino-cyclohexylamino	224
41	4-chlorophenyl	trans-4-(4-chlorophenylsulfonylamino)-cyclohexylamino	230
42	4-chlorophenyl	trans-4-ethoxycarbonylamino-cyclohexylamino	305 (dec.)
43	4-chlorophenyl	trans-4-benzoylaminocyclohexylamino	310
44	4-methylphenyl	dipropylamino	58
45	4-methylphenyl	butylamino	108
46	4-methylphenyl	thiomorpholino	185
47	4-methylphenyl	diethylamino	107
48	4-methylphenyl	2-hydroxyethylamino	164
49	4-methylphenyl	cis-2,6-dimethylmorpholino	135
50	4-methylphenyl	3-methoxypropylamino	oil

Example	R^3 (in formula I)	R^1R^2N- (in formula I)	M.p. (°C)
51	4-methylphenyl	perhydro-1-azepinyl	91
52	4-methylphenyl	di-(2-methoxyethyl)amino	oil
53	4-methylphenyl	isobutylamino	oil
54	4-methylphenyl	cyclopentylamino	130
55	4-methylphenyl	piperidino	125
56	4-methylphenyl	cyclopentylamino	190 (mes.)
57	4-methylphenyl	pyrrolidino	139
58	4-methylphenyl	di-(2-hydroxyethyl)amino	resin
59	4-methylphenyl	trans-4-hydroxycyclohexylamino	185
60	4-methylphenyl	(cyclopropylmethyl)amino	140
61	4-methylphenyl	cyclobutylamino	294
62	4-methylphenyl	4-methylcyclohexylamino	122
63	4-methylphenyl	N-methyl-N-cyclohexylamino	141
64	4-methylphenyl	cyclononylamino	oil
65	4-methylphenyl	2-isopropyl-5-methylcyclohexylamino	oil
66	4-methylphenyl	trans-2-hydroxycyclohexylamino	180
67	4-methylphenyl	3,3-dimethylpiperidino	79
68	4-methylphenyl	3-hydroxymethylpiperidino	140
69	4-methylphenyl	cyclopropylamino	110
70	4-methylphenyl	(R)-1-phenylethylamino	oil
71	4-methylphenyl	(S)-1-phenylethylamino	oil
72	3,4-dimethoxy-phenyl	cyclohexylamino	107
73	3,4-dimethoxy-phenyl	cyclopentylamino	237 (HCl)

Example	R^3 (in formula I)	R^1R^2N- (in formula I)	M.p. (°C)
74	3,4-dimethoxyphenyl	trans-4-hydroxycyclohexylamino	208 (HCl)
75	3,4-dimethoxyphenyl	4-hydroxy-4-phenylpiperidino	104
76	3,4-dimethoxyphenyl	4-hydroxybutylamino	216 (HCl)
77	3,4-dimethoxyphenyl	perhydro-1-azepinyl	oil
78	3,4-dimethoxyphenyl	butylamino	211 (HCl)
79	3,4-dimethoxyphenyl	dipropylamino	163 (HCl)
80	3,4-dimethoxyphenyl	cis-2,6-dimethylmorpholino	141
81	3-chlorophenyl	isobutylamino	89
82	3-chlorophenyl	cyclopentylamino	111
83	3-chlorophenyl	2,2,6,6-tetramethylpiperidin-4-ylamino	165
84	3-chlorophenyl	thiomorpholino	150
85	3-chlorophenyl	trans-4-hydroxycyclohexylamino	140
86	3-chlorophenyl	trans-4-hydroxycyclohexylamino	247 (mes.)
87	4-methoxyphenyl	methylamino	97
88	4-methoxyphenyl	2-methoxyethylamino	99
89	4-methoxyphenyl	isopentylamino	95
90	4-methoxyphenyl	trans-4-hydroxycyclohexylamino	175
91	4-methoxyphenyl	cyclopentylamino	110
92	4-methoxyphenyl	4-hydroxy-4-(4-chlorophenyl)piperidino	74
93	4-methoxyphenyl	5-hydroxy-1,5-dimethylhexylamino	oil

Example	R^3 (in formula I)	R^1R^2N- (in formula I)	M.p. (°C)
94	4-cyanophenyl	2-(2-chlorophenyl)ethylamino	157
95	4-cyanophenyl	3,4-dimethoxybenzylamino	177
96	4-cyanophenyl	trans-4-hydroxycyclohexylamino	233
97	3,5-dichlorophenyl	trans-4-hydroxycyclohexylamino	202
98	3,5-dichlorophenyl	cyclohexylamino	158
99	3,5-dichlorophenyl	N-methyl-N-(trans-4-hydroxycyclohexyl)amino	170
100	3,5-dichlorophenyl	4-hydroxybutylamino	113
101	3,4-dichlorophenyl	trans-4-hydroxycyclohexylamino	212
102	3,4-dichlorophenyl	cycloheptylamino	148
103	3,4-dichlorophenyl	4-hydroxybutylamino	148
104	2,4-dichlorophenyl	cyclopentylamino	101
105	2,4-dichlorophenyl	trans-4-hydroxycyclohexylamino	102
106	2,4-dichlorophenyl	4-hydroxybutylamino	141
107	2-chlorophenyl	trans-4-hydroxycyclohexylamino	176
108	2-chlorophenyl	3,4-dimethoxybenzylamino	oil
109	3-bromophenyl	trans-4-hydroxycyclohexylamino	88
110	3-bromophenyl	4-hydroxybutylamino	129
111	3-bromophenyl	cyclopentylamino	131
112	3,5-difluorophenyl	trans-4-hydroxycyclohexylamino	197
113	3,5-difluorophenyl	N-methyl-N-(pyridin-3-ylmethyl)amino	138
114	3,5-difluorophenyl	3,4-dimethoxybenzylamino	131

In the column "M.p.", the statement "(mes.)" means that the compound was prepared as methanesulfonic acid salt, and the statement "(HCl)" means that the compound was prepared as hydrochloride. The statement "(dec.)" means that the compound melted with decomposition.

Pharmacological investigations

Activation of soluble guanylate cyclase

The activation of soluble guanylate cyclase (sGC), which catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) and pyrophosphate, by the compounds according to the invention was quantified with the aid of an enzyme immunoassay (EIA) from Amersham. For this, the test substances were first incubated with sGC in microtiter plates and then the quantity of the resulting cGMP was determined.

The sGC employed had been isolated from bovine lung (see Methods in Enzymology, Volume 195, p. 377). The test solutions (100 µl per well) contained 50 mM triethanolamine (TEA) buffer (pH 7.5), 3 mM $MgCl_2$, 3 mM reduced glutathione (GSH), 0.1 mM GTP, 1 mM 3-isobutyl-1-methylxanthine (IBMX), suitably diluted enzyme solution and the test substance or, in the control experiments, solvent. The test substances were dissolved in dimethyl sulfoxide (DMSO) and the solution was diluted with DMSO/water such that the final concentration c of test substance in the test batch was 50 µM. The DMSO concentration in the test batch was 5% (v/v). The reaction was started by addition of the sGC. The reaction mix was incubated at 37°C for 15 to 20 minutes and then stopped by ice-cooling and addition of the stop reagent (50 mM EDTA, pH 8.0). An aliquot of 50 µl was taken and employed for the determination of the cGMP content using the acetylation protocol of the Amersham cGMP EIA kit. The absorption of the samples was measured at 450 nm (reference wavelength 620 nm) in a microtiter plate reading apparatus. The cGMP concentration was determined by means of a calibration curve, which was obtained under the same experimental conditions. The activation of the sGC by a test substance is given as n-fold stimulation of the basal enzyme activity which was found in the control experiments (with solvent instead of test substance), calculated according to the formula

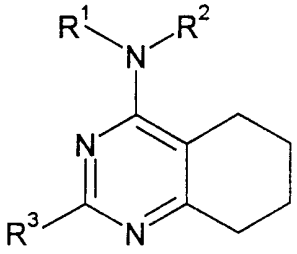
n-fold stimulation = $[cGMP]_{test\ substance}$ / $[cGMP]_{control}$.

The following results were obtained:

Compound of Example No.	n-fold stimulation (at c = 50 µM)
26	28
31	14
34	22
35	8
38	20
42	23
53	12
54	20
59	17
68	18
85	27
90	14
97	36
99	22

Patent claims

1. A compound of the formula I,



I

in which

R^1 and R^2, which are independent of one another and which can be identical or different, are hydrogen, or are (C_1-C_{10})-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxy, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl-$S(O)_m$-, (C_3-C_7)-cycloalkyl, phenyl, naphthyl and pyridyl, or are (C_3-C_9)-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, benzyl, hydroxy, amino, H-CO-O-, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-O-CO-O-, H-CO-NH-, (C_1-C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-, or are a residue of a 5-membered to 7-membered saturated heterocyclic ring which contains one or two identical or different hetero ring members from the group consisting of O, NR^{10} and $S(O)_m$ and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, hydroxy and aryl-(C_1-C_4)-alkyl-, but R^1 and R^2 cannot simultaneously be hydrogen,

or

the residue R^1R^2N- is a residue of a 5-membered to 7-membered saturated heterocyclic ring bonded via a ring nitrogen atom which in addition to the nitrogen atom bonded to the tetrahydroquinazoline ring can contain one further hetero ring member from the group consisting of O and $S(O)_m$ and which can be substituted by

one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, phenyl, hydroxy, (C_1-C_4)-alkoxy, hydroxy-(C_1-C_4)-alkyl- and $R^{11}R^{12}N$-,

where phenyl groups, naphthyl groups, pyridyl groups and benzyl groups present in R^1, R^2 and R^1R^2N- can be unsubstituted or substituted in the aromatic ring by one or more identical or different substituents from the group consisting of halogen, (C_1-C_4)-alkyl, phenyl, CF_3, NO_2, OH, -O-(C_1-C_4)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_4)-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, -NH-(C_1-C_4)-alkyl, -N((C_1-C_4)-alkyl)$_2$, -NH-CHO, -NH-CO-(C_1-C_4)-alkyl, CN, -CO-NH_2, -CO-NH-(C_1-C_4)-alkyl, -CO-N((C_1-C_4)-alkyl)$_2$, -CO-OH, -CO-O-(C_1-C_4)-alkyl, -CHO and -CO-(C_1-C_4)-alkyl;

R^3 is aryl, but cannot be unsubstituted phenyl;

R^{10} is hydrogen, (C_1-C_4)-alkyl, aryl-(C_1-C_4)-alkyl-, hydroxy-(C_1-C_4)-alkyl-, hydroxycarbonyl-(C_1-C_4)-alkyl-, ((C_1-C_4)-alkoxycarbonyl)-(C_1-C_4)-alkyl-, $R^{11}R^{12}N$-CO-(C_1-C_4)-alkyl-, R^{13}-SO_2- or aryl;

R^{11} and R^{12} are identical or different residues from the group consisting of hydrogen and (C_1-C_4)-alkyl;

R^{13} is (C_1-C_4)-alkyl, aryl or $R^{11}R^{12}N$-;

aryl is phenyl, naphthyl or heteroaryl which can all be substituted by one or more identical or different substituents from the group consisting of halogen, (C_1-C_4)-alkyl, phenyl, CF_3, NO_2, OH, -O-(C_1-C_4)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_4)-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, -NH-(C_1-C_4)-alkyl, -N((C_1-C_4)-alkyl)$_2$, -NH-CHO, -NH-CO-(C_1-C_4)-alkyl, CN, -CO-NH_2, -CO-NH-(C_1-C_4)-alkyl, -CO-N((C_1-C_4)-alkyl)$_2$, -CO-OH, -CO-O-(C_1-C_4)-alkyl, -CHO and -CO-(C_1-C_4)-alkyl;

heteroaryl is a residue of a monocyclic 5-membered or 6-membered aromatic heterocycle or of a bicyclic 8-membered to 10-membered aromatic heterocycle, each of which containing one or more identical or different ring heteroatoms from the group consisting of N, O and S;

m is 0, 1 or 2,

in all its stereoisomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts.

2. A compound of the formula I as claimed in claim 1, in which
one of the residues R^1 and R^2 is (C_1-C_8)-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxy, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl-$S(O)_m$-, (C_3-C_7)-cycloalkyl, phenyl and naphthyl, or is (C_3-C_9)-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, benzyl, hydroxy, amino, H-CO-O-, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-O-CO-O-, H-CO-NH-, (C_1-C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-,
and the other of the residues R^1 and R^2 is hydrogen, or is (C_1-C_8)-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxy, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl-$S(O)_m$-, (C_3-C_7)-cycloalkyl, phenyl and naphthyl, or is (C_3-C_9)-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, benzyl, hydroxy, amino, H-CO-O-, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-O-CO-O-, H-CO-NH-, (C_1-C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-,
where phenyl groups, naphthyl groups and benzyl groups present in R^1 and R^2 can be unsubstituted or substituted in the aromatic ring,
or R^1R^2N- is a residue of a 5-membered, 6-membered or 7-membered saturated heterocyclic ring bonded via a ring nitrogen atom which, in addition to the nitrogen atom bonded to the tetrahydroquinazoline ring, can contain one oxygen atom or one

group $S(O)_m$ as a further hetero ring member and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, hydroxy, (C_1-C_4)-alkoxy, hydroxy-(C_1-C_4)-alkyl- and $R^{11}R^{12}N$-,
in all its stereoisomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts.

3. A compound of the formula 1 as claimed in claim 1 and/or 2, in which
one of the residues R^1 and R^2 is (C_1-C_4)-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxy, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl-$S(O)_m$-, (C_3-C_7)-cycloalkyl, phenyl and naphthyl, or is (C_3-C_9)-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, benzyl, hydroxy, amino, H-CO-O-, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-O-CO-O-, H-CO-NH-, (C_1-C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-,
and the other of the residues R^1 and R^2 is hydrogen or is (C_1-C_4)-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxy, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl-$S(O)_m$-, (C_3-C_7)-cycloalkyl, phenyl and naphthyl,
where phenyl groups, naphthyl groups and benzyl groups present in R^1 and R^2 can be unsubstituted or substituted in the aromatic ring,
in all its stereoisomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts.

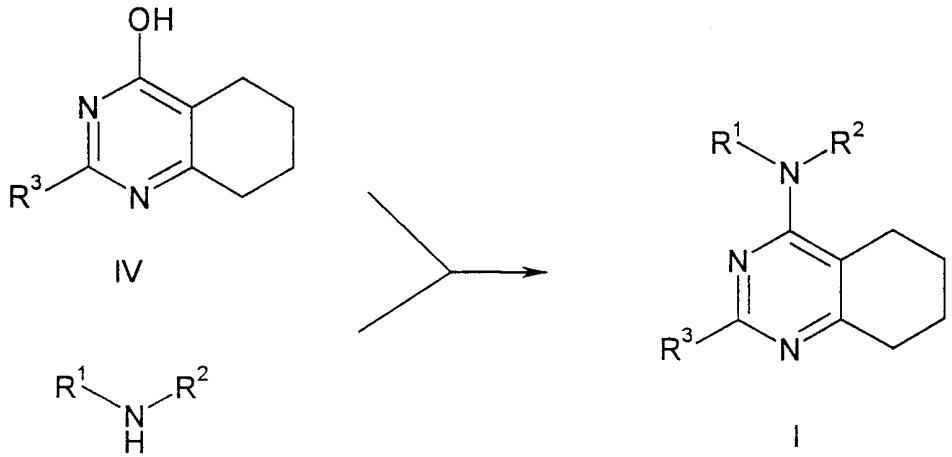
4. A compound of the formula I as claimed in one or more of claims 1 to 3, in which
one of the residues R^1 and R^2 is (C_3-C_9)-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, benzyl, hydroxy, amino, H-CO-O-, (C_1-C_4)-alkyl-CO-O-, (C_1-C_4)-alkyl-O-CO-O-, H-CO-NH-, (C_1-C_4)-alkyl-CO-NH-, (C_1-C_4)-alkyl-O-CO-NH-, phenyl-CO-NH-, (C_1-C_4)-alkyl-SO_2-NH- and phenyl-SO_2-NH-, were phenyl groups and benzyl groups present

in R^1 and R^2 can be unsubstituted or substituted in the aromatic ring, and the other of the residues R^1 and R^2 is hydrogen,
in all its stereoisomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts.

5. A compound of the formula I as claimed in claim 1 and/or 2, in which R^1R^2N- is a residue from the group consisting of piperidino, morpholino and thiomorpholino (and its S-oxide and S,S-dioxide),
in all its stereoisomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts.

6. A compound of the formula I as claimed in one or more of claims 1 to 5, in which R^3 is substituted phenyl,
in all its stereoisomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts.

7. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1 to 6 or a salt thereof, which comprises activating a 4-hydroxytetrahydroquinazoline of the formula IV and reacting it with an amine of the formula VI,



where R^1, R^2 and R^3 have the meanings indicated in claims 1 to 6.

8. A compound of the formula I and/or its physiologically acceptable salts as claimed in one or more of claims 1 to 6 for use as a pharmaceutical.

9. A pharmaceutical composition which comprises at least one compound of the formula I and/or a physiologically acceptable salt thereof as claimed in one or more of claims 1 to 6 and a physiologically acceptable carrier.

10. A compound of the formula I and/or a physiologically acceptable salt thereof as claimed in one or more of claims 1 to 6 for use as activator of soluble guanylate cyclase.

11. A compound of the formula I and/or a physiologically acceptable salt thereof as claimed in one or more of claims 1 to 6 for use in the therapy or prophylaxis of cardiovascular disorders, endothelial dysfunction, diastolic dysfunction, atherosclerosis, hypertension, angina pectoris, thrombosis, restenosis, myocardial infarct, stroke, cardiac insufficiency, pulmonary hypertension, erectile dysfunction, bronchial asthma, chronic renal insufficiency, diabetes or liver cirrhosis or for improving restricted learning capacity or memory power.

INTERNATIONAL SEARCH REPORT

Interna il Application No
PCT/EP 00/00468

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/94 A61K31/505 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 826 673 A (DAINIPPON) 4 March 1998 (1998-03-04) page 45 -page 47; claims ---	1,7-11
X	CHEMICAL ABSTRACTS, vol. 129, no. 5, 1998 Columbus, Ohio, US; abstract no. 54385e, page 640; XP002137815 abstract & JP 10 130150 A (DAINIPPON) 19 May 1998 (1998-05-19) --- -/--	1,7-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 May 2000	29/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 00/00468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 124, no. 7, 1996 Columbus, Ohio, US; abstract no. 87034q, page 1317; XP002137816 abstract & JP 07 228573 A (DAINIPPON) 29 August 1995 (1995-08-29)	1,7-11
A	US 3 346 452 A (R.W.CARNEY) 10 October 1967 (1967-10-10) column 13 -column 16	1,7-11

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

Internat al Application No
PCT/EP 00/00468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 826673 A	04-03-1998	AU 694647 B	23-07-1998
		AU 5287496 A	30-10-1996
		BR 9604894 A	14-07-1998
		NO 974685 A	12-12-1997
		NZ 304982 A	29-03-1999
		PL 322819 A	16-02-1998
		SK 137497 A	06-05-1998
		US 5972946 A	26-10-1999
		CA 2218033 A	17-10-1996
		CN 1186487 A	01-07-1998
		CZ 9703223 A	18-02-1998
		HU 9801688 A	29-03-1999
		WO 9632383 A	17-10-1996
		ZA 9602438 A	01-10-1996
JP 10130150 A	19-05-1998	NONE	
JP 07228573 A	29-08-1995	NONE	
US 3346452 A	10-10-1967	US 3322759 A	30-05-1967