COMMONWEALTH OF AUSTRALIA

P/00/001
Section 29

The Patents Act 1990

640505

PATENT REQUEST: CONVENTION PATENT

We, DR KARL THOMAE GmbH, being the person identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification

Full application details follow:-

Applicant:	DR KARL THOMAE GmbH
Address:	D-7950 Biberach an der Riss, Germany
Nominated Person:	DR KARL THOMAE GmbH
Address:	D-7950 Biberach an der Riss, Germany
Invention Title:	BENZIMIDAZOLES
Name(s) of actual Inventor(s):	Dr Berthold Narr; Dr Norbert Hauel; Dr Jacques Van Meel; Dr Wolfgang Wienen, Dr Michael Entzeroth and Dr Uwe Ries
Address for service in Australia:	CALLINAN LAWRIE, 278 High Street, Kew 3101, Victoria, Australia
Attorney Code:	CL

Convention Details

Application Number	Country	Country Code	Date of Application
P 4023369.3	Germany	DE	23 July 1990
P 4031287.9	Germany	DE	4 October 1990
P 4105324.9	Germany	DE	20 February 1991

D A T E D this 23rd day of July, 1991.

DR KARL THOMAE GmbH
By their Patent Attorneys:
CALLINAN LAWRIE

Jeffrey A. Ryder

028764 230791

CALLINAN LAWRIE
278 High Street, Kew
Victoria 3101, Australia

NOTICE OF ENTITLEMENT

We, DR KARL THOMAE, GmbH

of, D-7950 Biberach an der Riss, Germany

being the applicant in respect of Application No.

state the following:-

The person nominated for the grant of the patent:

(i) has entitlement from the actual inventor(s) by virtue of being a person who would, on the grant of a patent to said actual inventors, be entitled to have the patent assigned to it;

(ii) is the applicant of the basic applications

The basic applications listed:

(i) on the request form

are the first applications made in a Convention country in respect of the invention.

.....
Signature

23 JUL 1991
.....
Date

AU9181227

(12) PATENT ABRIDGMENT (11) Document No. AU-B-81227/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 640505

(54) Title
BENZIMIDAZOLES

International Patent Classification(s)

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	C07D 403/10	C07D 403/14	C07D 405/10	C07D 413/12
	C07D 413/14	C07D 417/10	C07D 417/14	C07D 471/04
	A61K 031/415	A61K 031/445		

(21) Application No. : **81227/91** (22) Application Date : **23.07.91**

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(43) Publication Date : **30.01.92**

(44) Publication Date of Accepted Application : **26.08.93**

(71) Applicant(s)
DR KARL THOMAE GMBH

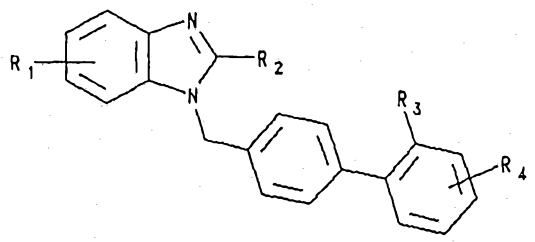
(72) Inventor(s)
DR BERTHOLD NARR; DR NORBERT HAUEL; DR JACQUES VAN MEEL; DR WOLFGANG WIENEN; DR MICHAEL ENTZEROTH; DR UWE RIES

(74) Attorney or Agent
CALLINAN LAWRIE , Private Bag 7, KEW VIC 3101

(56) Prior Art Documents
US 4880804
AU 64612/90 C07D 403/10
AU 629324 53013/90 C07D 403/10

(57) Claim

1. A compound of formula I



(I)

(wherein

R_1 represents a tetrahydrobenzimidazolyl or imidazopyridinyl group, a benzimidazolyl or benzoxazolyl group optionally substituted in the phenyl nucleus by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group, by a C_{1-3}-alkoxy or by a trifluoromethyl group, and in which the NH-group of the above-mentioned imidazole rings may additionally be substituted by a

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C_{1-6}-alkyl group or by a C_{3-7}-cycloalkyl group; an amino group substituted by a bicyclohexylcarbonyl or biphenylcarbonyl group; or a hydroxy(C_{5-7}-cycloalkyl)-aminocarbonyl group, which may additionally be substituted at the N-atom by a C_{1-3}-alkyl group; an aminocarbonylamino group substituted by a bicyclohexyl or biphenyl group and optionally also substituted by one or two C_{1-3}-alkyl groups at the N-atom; a 5-, 6- or 7-membered alkyleneimino or alkenyleneimino group optionally substituted by one or two C_{1-3}-alkyl groups or by a tetramethylene or pentamethylene group, in which a methylene group in the above mentioned alkylene and alkenylene moieties is replaced by a carbonyl or sulphonyl group; a 3,4,5,6-tetrahydro-2(1H)-pyrimidinone group optionally substituted by a C_{1-3}-alkyl or phenyl(C_{1-3}-alkyl) group; a straight-chained or branched hydroxy(C_{4-6}-alkyl)amino-carbonyl group; a maleic acid amido or maleic acid imido group optionally mono- or disubstituted by a C_{1-3}-alkyl group or by a phenyl group, in which the substituents may be identical or different; an imidazoline or imidazole group optionally substituted by a C_{1-6}-alkyl group or by a C_{3-7}-cycloalkyl group; an imidazolinedione group optionally substituted by a C_{1-3}-alkyl group, by a phenyl(C_{1-3}-alkyl) group or by a tetramethylene, pentamethylene or hexamethylene group; a C_{1-6}-alkylsulphonyloxy group; a benzenesulphonyloxy group optionally substituted by a C_{1-3}-alkyl group; a C_{1-3}-alkylamino or phenyl(C_{1-3}alkyl)amino group substituted by a C_{4-6}-alkylsulphonyl group or by a phenyl(C_{1-3}-alkyl)sulphonyl group; an amino or C_{1-3}alkylamino group substituted by a naphthalenesulphonyl group optionally substituted in the naphthalene ring by a di(C_{1-3}alkyl)-amino group or by one or two C_{1-3}-alkoxy groups; a C_{3-5}-alkoxy group substituted in the 3-, 4- or 5-position by an imidazolyl group; a C_{2-5}-alkoxy group substituted in the 2-, 3-, 4- or 5-position by a benzimidazolyl or tetrahydro-benzimidazolyl group; a pyridazin-3-one or dihydro-pyridazin-3-one group optionally substituted in the 2-position by an optionally phenyl-substituted C_{1-}

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$_3$alkyl group and optionally additionally substituted at a carbon atom by 1 or 2 C_{1-3} alkyl groups; a pyrrolidino, piperidino or hexamethyleneimino group substituted by two C_{1-3}-alkyl groups; a 7-nitrobenzofurazan-4-yl-amino(C_{2-3}alkanoyl)amino group; a heptamethyleneimino, 1H,3H-quinazolin-2,4-dion-3-yl, pentamethylene-oxazolin-2-yl, benzofuran-carbonylamino or 7-nitro-benzofurazan-4-yl-amino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent an amino group substituted by a phenylsulphonyl, cyclohexylmethylaminocarbonyl, 2-carboxycyclohexyl-methylcarbonyl, 2-tert.butoxycarbonyl-cyclohexylmethyl-carbonyl, 2-carboxy-3,4,5,6-tetrahydrobenzoyl, N-methyl-phenylaminocarbonyl or 3-cyclohexylpropyl group; a methylamino group substituted by a propylsulphonyl, phenylsulphonyl, methylphenylsulphonyl or chlorophenyl-sulphonyl group; an n-pentylamino group substituted by a phenylsulphonyl or methoxyphenylsulphonyl group; an n-propylamino group substituted by a methylphenylsulphonyl or methoxyphenylsulphonyl group; an isopropylamino group substituted by a benzoyl or chlorophenylsulphonyl group; an N-acetyl-cyclohexylmethylamino, 3,4,5,6-tetrahydro-phthalimido, hexahydrohomophthalimido, N-methanesulphonyl-2-phenylethylamino, N-chlorophenyl-sulphonyl-benzylamino, piperidino, 4-methyl-piperidino or hexamethyleneimino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent a 2-oxo-1,2-dihydro-3,4-tetramethylene-pyrrolidin-1-yl, 3-carboxy-propionyl or 3-carboxy-2-methyl-propionyl group, and

where R_3 represents a carboxy group and R_2 represents a methyl, ethyl, n-propyl, n-butyl or methylmercapto group, R_1 in the 6-position may also represent a pyrrolidino-carbonylamino group, and

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where R_3 represents a tetrazolyl group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent an n-pentylamino group substituted by a methyl-aminocarbonyl or cyclohexylaminocarbonyl group and R_1 in the 6-position may represent a 3,3-dimethyl-glutaric acid imido or 4,4-tetramethylene-glutaric acid imido group, and

where R_3 represents a tetrazolyl group and R_2 represents an ethyl or n-propyl group, R_1 in the 6-position may also represent an N-benzenesulphonyl-methylamino group, and

where R_3 represents a tert.butoxycarbonyl group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent a 2-carboxycyclohexylmethylcarbonylamino or pyrrolidinocarbonylamino group;

R_2 represents a hydrogen atom or a straight-chained or branched C_{1-5}-alkyl group in which a methylene group may optionally be replaced by a sulphur atom;

R_3 represents a carboxy, cyano, 1H-tetrazolyl or 1-triphenylmethyl-tetrazolyl group or a (C_{1-4}alkoxy)-carbonyl group; and

R_4 represents a hydrogen, fluorine, chlorine or bromine atom);

and isomers and salts thereof.

8. A method of treatment of the human or non-human animal body to combat hypertension, cardiac insufficiency, ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), cardiac insufficiency progression following myocardial infarction, diabetic nephropathy, glaucoma, gastrointestinal diseases and bladder diseases said method comprising administering to said body a compound of formula I as claimed in any one of claims 1 to 4 or a physiologically acceptable salt thereof.

P/00/011
Regulation 3.2

AUSTRALIA 640505

PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

TO BE COMPLETED BY APPLICANT

Name of Applicant: DR KARL THOMAE GmbH

Actual Inventor(s): Dr Berthold Narr; Dr Norbert Hauel, Dr Jacques Van Meel; Dr Wolfgang Wienen, Dr Michael Entzeroth and Dr Uwe Ries

Address for Service: CALLINAN LAWRIE, 278 High Street, Kew, 3101, Victoria, Australia

Invention Title: "BENZIMIDAZOLES"

The following statement is a full description of this invention, including the best method of performing it known to me:-

56779/000.562

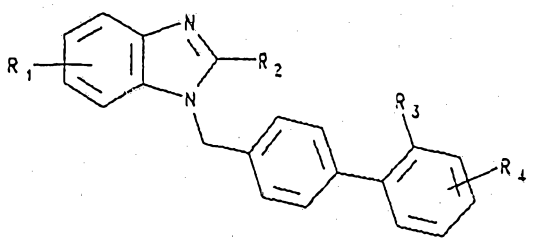
Benzimidazoles

The present invention relates to new benzimidazoles, processes for their preparation and pharmaceutical compositions containing them.

US-A-4,880,804 describes inter alia 4'-[(2-alkyl-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acids and 4'-[(2-alkyl-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyls which are substituted in the benzimidazole ring by an alkanoylaminomethyl group and which are angiotension-II antagonists.

It has now been found that certain new benzimidazoles are even more useful angiotensin antagonists, particularly angiotensin-II antagonists.

Thus, according to one aspect the present invention provides compounds of formula I



(I)

(wherein
R_1 represents a tetrahydrobenzimidazolyl or imidazo-pyridinyl group, a benzimidazolyl or benzoxazolyl group optionally substituted in the phenyl nucleus by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group, by a C_{1-3}-alkoxy group or by a trifluoromethyl group, and in which the NH-group of the above-mentioned imidazole rings may additionally be substituted by a C_{1-6}-alkyl group or by a C_{3-7}-cycloalkyl group; an amino

group substituted by a bicyclohexylcarbonyl or biphenylcarbonyl group; or a hydroxy(C_{5-7}-cycloalkyl)-amino carbonyl group which may additionally be substituted at the N-atom by a C_{1-3}-alkyl group; an aminocarbonylamino group substituted by a bicyclohexyl or biphenyl group and optionally also substituted by one or two C_{1-3}-alkyl groups at the N-atom; a 5-, 6- or 7-membered alkyleneimino or alkenyleneimino group optionally substituted by one or two C_{1-3}-alkyl groups or by a tetramethylene or pentamethylene group, in which a methylene group in the above mentioned alkylene and alkenylene moieties is replaced by a carbonyl or sulphonyl group; a 3,4,5,6-tetrahydro-2(1H)-pyrimidinone group optionally substituted by a C_{1-3}-alkyl or phenyl(C_{1-3}-alkyl) group; a straight-chained or branched hydroxy(C_{4-6}-alkyl)amino carbonyl group; a maleic acid amido or maleic acid imido group optionally mono- or disubstituted by a C_{1-3}-alkyl or by a phenyl group, in which the substituents may be identical or different; an imidazoline or imidazole group optionally substituted by a C_{1-6}-alkyl group or by a C_{3-7}-cycloalkyl group; an imidazolidinedione group optionally substituted by a C_{1-3}-alkyl group, by a phenyl(C_{1-3}-alkyl) group or by a tetramethylene, pentamethylene or hexamethylene group; a C_{1-6}-alkylsulphonyloxy group; a benzenesulphonyloxy group optionally substituted by a C_{1-3}-alkyl group; a C_{1-3}-alkylamino or phenyl (C_{1-3}-alkyl)amino group substituted by a C_{4-6}-alkylsulphonyl group or by a phenyl(C_{1-3}-alkyl)sulphonyl group; an amino or C_{1-3}-alkylamino group substituted by a naphthalenesulphonyl group optionally substituted in the naphthalene ring by a di(C_{1-3}-alkyl)amino group or by one or two C_{1-3}-alkoxy groups; a C_{3-5}-alkoxy group substituted in the 3-, 4- or 5-position by an imidazolyl group; a C_{2-5}-alkoxy group substituted in the 2-, 3-, 4- or 5-position by a benzimidazolyl or tetrahydrobenzimidazolyl group; a pyridazin-3-one or dihydro-pyridazin-3-one group optionally substituted in

the 2-position by an optionally phenyl-substituted C_{1-3}-alkyl group and optionally additionally substituted at a carbon atom by 1 or 2 C_{1-3}-alkyl groups; a pyrrolidino, piperidino or hexamethyleneimino group substituted by two C_{1-3}-alkyl groups; a 7-nitrobenzofurazan-4-yl-amino(C_{2-3}-alkanoyl)amino group; a heptamethyleneimino, 1H,3H-quinazolin-2,4-dion-3-yl, pentamethylene-oxazolin-2-yl, benzofuran-carbonylamino or 7-nitro-benzofurazan-4-yl-amino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent an amino group substituted by a phenylsulphonyl, cyclohexylmethylaminocarbonyl, 2-carboxycyclohexyl-methylcarbonyl, 2-tert.butoxycarbonyl-cyclohexylmethyl-carbonyl, 2-carboxy-3,4,5,6-tetrahydrobenzoyl, N-methyl-phenylaminocarbonyl or 3-cyclohexylpropyl group; a methylamino group substituted by a propylsulphonyl, phenylsulphonyl, methylphenylsulphonyl or chlorophenyl-sulphonyl group; an n-pentylamino group substituted by a phenylsulphonyl or methoxyphenylsulphonyl group; an n-propylamino group substituted by a methylphenylsulphonyl or methoxyphenylsulphonyl group; an isopropylamino group substituted by a benzoyl or chlorophenylsulphonyl group; an N-acetyl-cyclohexylmethylamino, 3,4,5,6-tetrahydro-phthalimido, hexahydrohomophthalimido, N-methanesulphonyl-2-phenylethylamino, N-chlorophenyl-sulphonyl-benzylamino, piperidino, 4-methyl-piperidino or hexamethyleneimino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent a 2-oxo-1,2-dihydro-3,4-tetramethylene-pyrrolidin-1-yl, 3-carboxy-propionyl or 3-carboxy-2-methyl-propionyl group, and

where R_3 represents a carboxy group and R_2 represents a

methyl, ethyl, n-propyl, n-butyl or methylmercapto group, R_1 in the 6-position may also represent a pyrrolidino-carbonylamino group, and

where R_3 represents a tetrazolyl group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent an n-pentylamino group substituted by a methyl-aminocarbonyl or cyclohexylaminocarbonyl group, and R_1 in the 6-position may also represent a 3,3-dimethyl-glutaric acid imido or 4,4-tetramethylene-glutaric acid imido group, and

where R_3 represents a tetrazolyl group and R_2 represents an ethyl or n-propyl group, R_1 in the 6-position may also represent an N-benzenesulphonyl-methylamino group, and

where R_3 represents a tert.butoxycarbonyl group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent a 2-carboxycyclohexylmethylcarbonylamino or pyrrolidinocarbonylamino group;

R_2 represents a hydrogen atom or a straight-chained or branched C_{1-5}-alkyl group in which a methylene group may optionally be replaced by a sulphur atom;

R_3 represents a carboxy, cyano, 1H-tetrazolyl or 1-triphenylmethyl-tetrazolyl group or a (C_{1-4}-alkoxy)-carbonyl group; and

R_4 represents a hydrogen, fluorine, chlorine or bromine atom);

and isomers, especially the 1-,3-isomer mixtures, and salts thereof, in particular, for pharmaceutical use the physiologically acceptable salts thereof with organic or inorganic acids or bases.

The following are examples of the definitions of the

groups R_1 and R_2 as mentioned hereinbefore:

R_1 may represent a benzimidazol-2-yl, 1-methyl-benzimidazol-2-yl, 1-ethyl-benzimidazol-2-yl, 1-n-propyl-benzimidazol-2-yl, 1-isopropyl-benzimidazol-2-yl, 1-n-butyl-benzimidazol-2-yl, 1-n-pentyl-benzimidazol-2-yl, 1-n-hexyl-benzimidazol-2-yl, 1-cyclopropyl-benzimidazol-2-yl, 1-cyclopentyl-benzimidazol-2-yl, 1-cyclohexyl-benzimidazol-2-yl, 1-cycloheptyl-benzimidazol-2-yl, 1,5-dimethyl-benzimidazol-2-yl, 1,6-dimethyl-benzimidazol-2-yl, 1-methyl-5-methoxy-benzimidazol-2-yl, 1-methyl-5-fluoro-benzimidazol-2-yl, 1-methyl-5-chloro-benzimidazol-2-yl, 1-methyl-5-bromo-benzimidazol-2-yl, 1-methyl-5-trifluoromethyl-benzimidazol-2-yl, tetrahydro-benzimidazol-2-yl, 1-methyl-tetrahydro-benzimidazol-2-yl, 1-ethyl-tetrahydro-benzimidazol-2-yl, 1-n-propyl-tetrahydro-benzimidazol-2-yl, 1-isopropyl-tetrahydro-benzimidazol-2-yl, 1-n-butyl-tetrahydro-benzimidazol-2-yl, 1-n-pentyl-tetrahydro-benzimidazol-2-yl, 1-n-hexyl-tetrahydro-benzimidazol-2-yl, 1-cyclopropyl-tetrahydro-benzimidazol-2-yl, 1-cyclopentyl-tetrahydro-benzimidazol-2-yl, 1-cyclohexyl-tetrahydro-benzimidazol-2-yl, 1-cycloheptyl-tetrahydro-benzimidazol-2-yl, benzoxazol-2-yl, 5-methyl-benzoxazol-2-yl, 5-methoxy-benzoxazol-2-yl, 5-trifluoromethyl-benzoxazol-2-yl, 5-fluoro-benzoxazol-2-yl, 5-chloro-benzoxazol-2-yl, 5-bromo-benzoxazol-2-yl, 4-biphenylyl-carbonylamino, 4-cyclohexylcarbonylamino, N-methyl-4-biphenylylcarbonylamino, N-ethyl-4-cyclohexylcarbonyl-amino, N-n-propyl-4-biphenylylcarbonylamino, N-isopropyl-4-cyclohexylcarbonylamino, 2-hydroxy-cyclopentylamino, 2-hydroxy-cyclohexylamino, 2-hydroxy-cycloheptylamino, 3-hydroxy-cyclopentylamino, 3-hydroxy-cyclohexylamino, 3-hydroxy-cycloheptylamino, 4-hydroxy-cyclohexylamino, 4-hydroxy-cycloheptylamino, N-methyl-2-hydroxy-cyclopentylamino, N-ethyl-2-hydroxy-cyclohexylamino, N-isopropyl-2-hydroxy-cycloheptylamino,

N-methyl-3-hydroxy-cyclopentylamino, N-ethyl-3-hydroxy-cyclohexylamino, N-n-propyl-3-hydroxy-cycloheptylamino, N-methyl-4-hydroxy-cyclohexylamino, N-ethyl-4-hydroxy-cycloheptylamino, 4-biphenylylaminocarbonylamino, 4-bicyclohexylaminocarbonylamino, N-(4-biphenylylamino-carbonyl)-methylamino, N-(4-bicyclohexylaminocarbonyl)-methylamino, N-(methyl-4-biphenylylaminocarbonyl)-methylamino, N-(methyl-4-bicyclohexylaminocarbonyl)-methylamino, N-(4-biphenylylaminocarbonyl)-ethylamino, N-(4-bicyclohexylaminocarbonyl)-isopropylamino, N-(ethyl-4-biphenylylaminocarbonyl)-methylamino, N-(methyl-4-bicyclohexylaminocarbonyl)-ethylamino, pyrrolidin-2-on-1-yl, piperidin-2-on-1-yl, hexamethyleneimino-2-on-1-yl, propanesultam-1-yl, butanesultam-1-yl, pentanesultam-1-yl, 3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-methyl-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1yl, 3-ethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-n-propyl-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-isopropyl-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-(2-phenylethyl)-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-(3-phenylpropyl)-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 4-hydroxybutylamino, 5-hydroxypentylamino, 6-hydroxy-hexylamino, maleic acid imido, 2-methyl-maleic acid imido, 2-phenyl-maleic acid imido, 2,3-dimethyl-maleic acid imido, 2,3-diphenyl-maleic acid imido, 2-methyl-maleic acid amido, 3-methyl-maleic acid amido, 2,3-dimethyl-maleic acid amido, 2-phenyl-maleic acid amido, 3-phenyl-maleic acid amido, 2,3-diphenyl-maleic acid amido, 3-methyl-2-phenyl-maleic acid amido, 2-methyl-3-phenyl-maleic acid amido, imidazolin-2-yl, 1-methyl-imidazolin-2-yl, 1-ethyl-imidazolin-2-yl, 1-propyl-imidazolin-2-yl, imidazolidin-2,4-dion-3-yl, 5-methyl-imidazolidin-2,4-dion-3-yl, 5-ethyl-imidazolidin-2,4-dion-3-yl, 5-n-propyl-imidazolidin-2,4-dion-3-yl, 5-benzyl-imidazolidin-2,4-dion-3-yl, 5-(2-phenylethyl)-

imidazolidin-2,4-dion-3-yl, 5-(3-phenylpropyl)-imidazolidin-2,4-dion-3-yl, 5,5-tetramethylene-imidazolidin-2,4-dion-3-yl, 5,5-pentamethylene-imidazolidin-2,4-dion-3-yl, 5,5-hexamethylene-imidazolidin-2,4-dion-3-yl, 5,5-dimethyl-imidazolidin-2,4-dion-3-yl, 5,5-diethyl-imidazolidin-2,4-dion-3-yl, methanesulphonyloxy, ethanesulphonyloxy, propanesulphonyloxy, butanesulphonyloxy, pentanesulphonyloxy, hexanesulphonyloxy, benzenesulphonyloxy, p-toluenesulphonyloxy, N-n-butanesulphonyl-methylamino, N-n-pentanesulphonyl-methylamino, N-n-hexanesulphonyl-methylamino, N-phenylmethanesulphonyl-methylamino, N-(2-phenylethanesulphonyl)-methylamino, N-(3-phenylpropanesulphonyl)-methylamino, N-n-butanesulphonyl-ethylamino, N-n-pentanesulphonyl-isopropylamino, N-n-hexanesulphonyl-ethylamino, N-phenylmethanesulphonyl-ethylamino, N-(2-phenylethanesulphonyl)-n-propylamino, N-(3-phenylpropanesulphonyl)-ethylamino, naphthalen-1-sulphonylamino, naphthalen-2-sulphonylamino, 5-dimethylamino-naphthalen-1-sulphonylamino, N-(naphthalen-1-sulphonyl)-methylamino, N-(naphthalen-2-sulphonyl)-ethylamino, N-(5-dimethylamino-naphthalen-1-sulphonyl)-methylamino, N-(5-methoxynaphthalen-1-sulphonyl)-methylamino, N-(5,6-dimethoxy-naphthalen-2-sulphonyl)-ethylamino, 3-(imidazol-1-yl)-propoxy, 4-(imidazol-1-yl)-butoxy, 5-(imidazol-1-yl)-pentoxy, 2-(benzimidazol-1-yl)-ethoxy, 3-(benzimidazol-1-yl)-propoxy, 4-(benzimidazol-1-yl)-butoxy, 5-(benzimidazol-1-yl)-pentoxy, 2-(tetrahydrobenzimidazol-1-yl)-ethoxy, 3-(tetrahydrobenzimidazol-1-yl)-propoxy, 4-(tetrahydrobenzimidazol-1-yl)-butoxy, 5-(tetrahydrobenzimidazol-1-yl)-pentoxy, 4,5-dihydro-2H-pyridazin-3-on-6-yl, 2-methyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2-ethyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2-n-propyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2-isopropyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2-benzyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2-(2-phenylethyl)-4,5-dihydro-2H-pyridazin-3-

on-6-yl, 2-(3-phenylpropyl)-4,5-dihydro-2H-pyridazin-3-on-6-yl, 4-methyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 5-methyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 4,4-dimethyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 5,5-dimethyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 4,5-dimethyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2,4-dimethyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2,5-dimethyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2,4,5-trimethyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2,4,4-trimethyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2,5,5-trimethyl-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2H-pyridazin-3-on-6-yl, 2-methyl-2H-pyridazin-3-on-6-yl, 2-ethyl-2H-pyridazin-3-on-6-yl, 2-n-propyl-2H-pyridazin-3-on-6-yl, 2-isopropyl-2H-pyridazin-3-on-6-yl, 2-benzyl-2H-pyridazin-3-on-6-yl, 2-(2-phenylethyl)-2H-pyridazin-3-on-6-yl, 2-(3-phenylpropyl)-2H-pyridazin-3-on-6-yl, 4-methyl-2H-pyridazin-3-on-6-yl, 5-methyl-2H-pyridazin-3-on-6-yl, 4,5-dimethyl-2H-pyridazin-3-on-6-yl, 2,4-dimethyl-2H-pyridazin-3-on-6-yl, 2,5-dimethyl-2H-pyridazin-3-on-6-yl, 2,4,5-trimethyl-2H-pyridazin-3-on-6-yl, 3,3-dimethyl-pyrrolidino, 3,4-dimethyl-pyrrolidino, 3,3-dimethyl-piperidino, 3,4-dimethylpiperidino, 4,4-dimethyl-piperidino, 3,3-dimethyl-hexamethyleneimino, 3,4-dimethyl-hexamethyleneimino, 4,4-dimethylhexamethyleneimino, 3,5-dimethyl-hexamethyleneimino, phenylsulphonylamino, cyclohexylmethylaminocarbonylamino, 2-methylamino-benzoylamino, 2-carboxy-cyclohexylmethylcarbonylamino, 2-tert.butoxycarbonyl-cyclohexylmethylcarbonylamino, 2-carboxy-3,4,5,6-tetrahydrobenzoylamino, 3-cyclohexylpropylamino, N-propylsulphonyl-methylamino, N-phenylsulphonyl-methylamino, N-(4-methylphenylsulphonyl)-methylamino, N-(4-chlorophenylsulphonyl)-methylamino, N-phenylsulphonyl-n-pentylamino, N-(4-methoxyphenylsulphonyl)-n-pentylamino, N-(4-methylphenylsulphonyl)-n-propylamino, N-(4-methoxyphenylsulphonyl)-n-propylamino, N-benzoyl-isopropylamino, N-(4-chlorophenylsulphonyl)-isopropyl-

amino, N-acetyl-cyclohexylmethylamino, 3,4,5,6-tetrahydrophthalimido, hexahydrophthalimido, N-methanesulphonyl-2-phenylethylamino, N-chlorophenylsulphonyl-benzylamino, piperidino, 4-methyl-piperidino, hexamethyleneimino, 3-carboxy-propionyl, 3-carboxy-2-methyl-propionyl, pyrrolidinocarbonylamino, N-methylaminocarbonyl-n-pentylamino, N-cyclohexylamino-carbonyl-n-pentylamino, 3,3-dimethyl-glutaric acid imido, 4,4-tetramethylene-glutaric acid imido, 2-carboxy-cyclohexylmethylcarbonylamino, 1-n-butyl-imidazolin-2-yl, 1-n-pentyl-imidazolin-2-yl, 1-n-hexyl-imidazolin-2-yl, 1-cyclopropyl-imidazolin-2-yl, 1-cyclobutyl-imidazolin-2-yl, 1-cyclohexyl-imidazolin-2-yl, 1-cycloheptyl-imidazolin-2-yl, imidazol-2-yl, 1-methyl-imidazol-2-yl, 1-ethyl-imidazol-2-yl, 1-propyl-imidazol-2-yl, 1-n-butyl-imidazol-2-yl, 1-n-pentyl-imidazol-2-yl, 1-n-hexyl-imidazol-2-yl, 1-cyclopropyl-imidazol-2-yl, 1-cyclobutyl-imidazol-2-yl, 1-cyclohexyl-imidazol-2-yl or 1-cycloheptyl-imidazol-2-yl group; and

R_2 may represent a hydrogen atom, a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert.-butyl, n-pentyl, 1-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-ethylpropyl, 1,1-diethylethyl, methylmercaptomethyl, 2-methylmercapto-ethyl, 3-methylmercaptopropyl or 4-methylmercaptobutyl group.

Preferred compounds according to the invention include those of formula I wherein

R_1 represents a tetrahydrobenzimidazolyl or imidazopyridinyl group, a benzimidazolyl group optionally substituted in the phenyl nucleus by a fluorine, chlorine or bromine atom or by a methyl, methoxy or trifluoromethyl group, and in which the NH-group of the above-mentioned imidazole rings may additionally be substituted by a C_{1-6}-alkyl group or by a

C_{3-6}-cycloalkyl group; a benzoxazol-2-yl group optionally substituted by a methyl group; an amino group substituted by a bicyclohexylcarbonyl, biphenylcarbonyl or benzofuryl-2-carbonyl group; an aminocarbonylamino group substituted in the 3-position by a bicyclohexyl or biphenyl group; a 5-, 6- or 7-membered alkyleneimino or alkenyleneimino group optionally substituted by one or two methyl groups or by a tetramethylene or pentamethylene group wherein a methylene group is replaced by a carbonyl or sulphonyl group; a 3,4,5,6-tetrahydro-2(1H)-pyrimidinone group optionally substituted by a methyl or benzyl group; a hydroxy(C_4-alkyl)aminocarbonyl group, a maleic acid amido or maleic acid imido group optionally substituted by one or two substituents which may be the same or different selected from methyl and phenyl groups; an imidazolin-2-yl or imidazol-2-yl group substituted in the 1-position by a C_{1-6}-alkyl group or by a C_{3-7}-cycloalkyl group; an imidazolidinedione group optionally substituted by a methyl, benzyl, tetramethylene or pentamethylene group; a methylamino or benzylamino group substituted by a butanesulphonyl group or by a phenylmethanesulphonyl group; an amino or methylamino group substituted by a naphthalenesulphonyl group in which the naphthalene ring may be substituted by a dimethylamino group or by 2 methoxy groups, a pyridazin-3-one or dihydro-pyridazin-3-one group optionally substituted by a methyl or benzyl group; a pyrrolidino, piperidino or hexamethyleneimino group substituted by two methyl groups; a heptamethyleneimino, 1H,3H-quinazolin-2,4-dion-3-yl, hydroxycyclohexylamino-carbonyl, 4,5-pentamethylene-oxazolin-2-yl, 7-nitro-benzofurazan-4-yl-amino or 7-nitro-benzofurazan-4-yl-aminopropionylamino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent an amino group substituted by a phenylsulphonyl,

cyclohexylmethylaminocarbonyl, 2-carboxycyclohexyl-methylcarbonyl, 2-tert.-butoxycarbonyl-cyclohexyl-methylcarbonyl, 2-carboxy-3,4,5,6-tetrahydrobenzoyl, N-methyl-phenylaminocarbonyl or 3-cyclohexylpropyl group; a methylamino group substituted by a propylsulphonyl, phenylsulphonyl, 4-methylphenylsulphonyl or 4-chlorophenylsulphonyl group; an n-pentylamino group substituted by a phenylsulphonyl or 4-methoxyphenyl-sulphonyl group; an n-propylamino group substituted by a 4-methylphenylsulphonyl or 4-methoxyphenylsulphonyl group; an isopropylamino group substituted by a benzoyl or 4-chlorophenylsulphonyl group, an N-acetyl-cyclohexylmethylamino, 3,4,5,6-tetrahydrophthalimido, hexahydrohomophthalimido, N-methanesulphonyl-2-phenylethylamino, N-(4-chlorophenylsulphonyl)-benzylamino, piperidino, 4-methyl-piperidino or hexamethyleneimino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent a 2-oxo-1,2-dihydro-3,4-tetramethylene-pyrrolidin-1-yl, 3-carboxy-propionyl or 3-carboxy-2-methyl-propionyl group, and

where R_3 represents a carboxy group and R_2 represents a methyl, ethyl, n-propyl, n-butyl or methylmercapto group, R_1 in the 6-position may also represent a pyrrolidino-carbonylamino group, and

where R_3 represents a tetrazolyl group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent an n-pentylamino group substituted by a methylaminocarbonyl or cyclohexylaminocarbonyl group and R_1 in the 6-position may also represent a 3,3-dimethyl-glutaric acid imido or 4,4-tetramethylene-glutaric acid imido group, and

where R_3 represents a tetrazolyl group and R_2 represents an ethyl or n-propyl group, R_1 in the 6-position may also represent an N-benzenesulphonyl-methylamino group, and

where R_3 represents a tert.butoxycarbonyl group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent a 2-carboxy-cyclohexylmethylcarbonylamino or pyrrolidinocarbonylamino group;

R_2 represents a hydrogen atom or a straight-chained or branched C_{1-4}-alkyl group in which a methylene group may be replaced by a sulphur atom;

R_3 represents a carboxy, cyano, 1H-tetrazolyl or 1-triphenylmethyl-tetrazolyl group or a (C_{1-4}-alkoxy)-carbonyl group; and

R_4 represents a hydrogen, fluorine, chlorine or bromine atom;

and isomers and salts thereof, especially the 1-, 3-isomer mixtures thereof, and particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

Particularly preferred compounds according to the invention include those of formula I wherein

R_1 in the 6-position represents a 1-methylbenzimidazol-2-yl, 3,4,5,6-tetrahydro-phthalimino, 2,3-diphenyl-maleic acid imido, 2,3-dimethyl-maleic acid imido, N-phenyl-methanesulphonyl-methylamino, 2-oxo-pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, 2-oxo-hexamethyleneimino, 2-oxo-3,4-tetramethylene-pyrrolidin-1-yl, 3,3-dimethylglutarimido, N-methylaminocarbonyl-n-pentylamino, propanesultam-1-yl or butanesultam-1-yl group;

R_2 represents a methyl, ethyl, n-propyl or n-butyl group;

R_3 represents a carboxy or 1H-tetrazolyl group; and

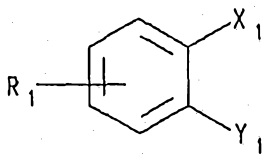
R_4 represents a hydrogen atom;

and the isomers and salts, especially the 1-,3- isomer mixtures thereof and particularly the physiologically acceptable addition salts thereof with organic or inorganic acids or bases.

Although the present invention relates to new compounds of formula I, the corresponding cyano, tert.-butoxycarbonyl and triphenylmethyl compounds, in particular, represent valuable intermediates which can readily be converted to one of the pharmacologically active compounds.

According to a further aspect the invention also provides a process for the preparation of compounds of the invention, said process comprising at least one of the following steps:

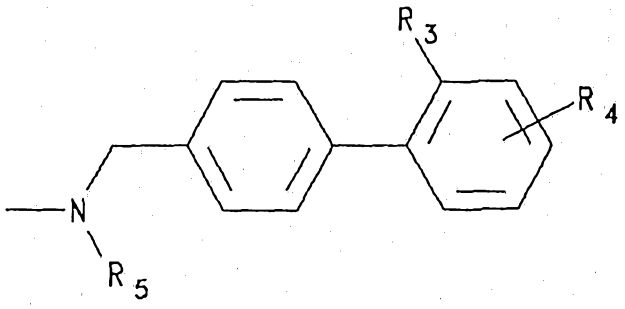
a) cyclising a compound of formula II



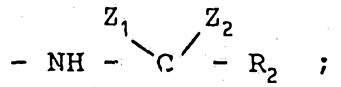
(II)

(wherein
R_1 is as hereinbefore defined;

one of the groups X_1 or Y_1 represents a group of formula

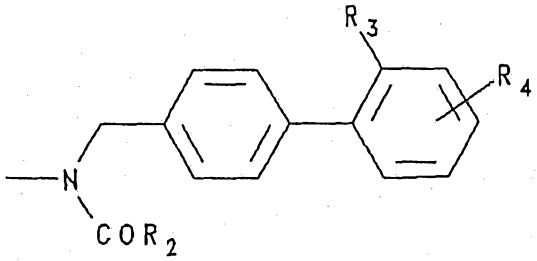


and the other group X_1 or Y_1 represents a group of formula

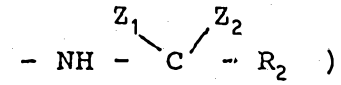


;

R_2, R_3 and R_4 are as hereinbefore defined;
R_5 represents a hydrogen atom or an R_2CO group;
Z_1 and Z_2, which may be the same or different, represent optionally substituted amino groups or hydroxy or mercapto groups optionally substituted by lower alkyl (e.g. C_{1-6}-alkyl) groups, or
Z_1 and Z_2 together represent an oxygen or sulphur atom, an imino group optionally substituted by a C_{1-3}-alkyl group, or a C_{2-3}-alkylenedioxy or C_{2-3}alkylenedithio group, with the proviso that one of the groups X_1 or Y_1 must represent a group of formula



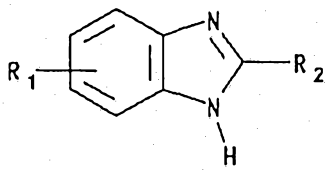
or



) or an N-oxide thereof

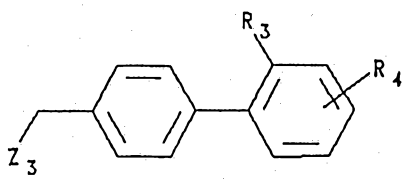
and subsequently if necessary reducing the cyclized N-oxide product;

b) reacting a benzimidazole of formula III



(III)

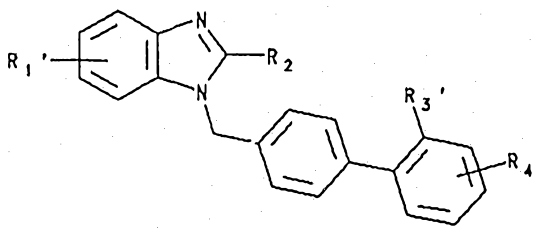
(wherein
R_1 and R_2 are as hereinbefore defined) with a biphenyl compound of formula IV



(IV)

(wherein
R_3 and R_4 are as hereinbefore defined; and
Z_3 represents a nucleophilic leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom, or a substituted sulphonyloxy group, e.g. a methanesulphonyloxy, phenylsulphonyloxy or p-toluenesulphonyloxy group);

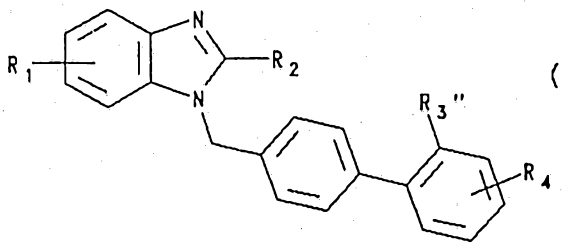
c) (to prepare a compound of formula I wherein R_3 represents a carboxy group) converting a compound of formula V



(V)

(wherein
R_2 and R_4 are as hereinbefore defined;
R_1' is a group R_1 as hereinbefore defined or a 3-((C_{1-3}-alkoxy)carbonyl)propionyl or 3-((C_{1-3}-alkoxy)carbonyl)-2-methylpropionyl group; and
R_3' represents a group which may be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis) into a corresponding carboxy compound;

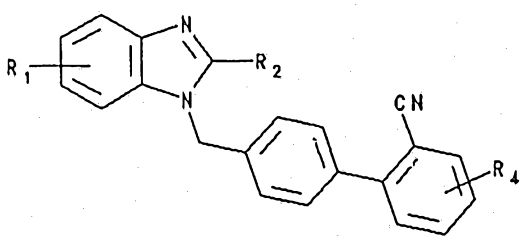
d) (to prepare a compound of formula I wherein R_3 represents a 1H-tetrazolyl group) cleaving a protecting group from a compound of formula VI



(VI)

(wherein
R_1, R_2 and R_4 are as hereinbefore defined; and
R_3" represents a 1H-tetrazolyl group protected in the 1- or 3-position by a protecting group);

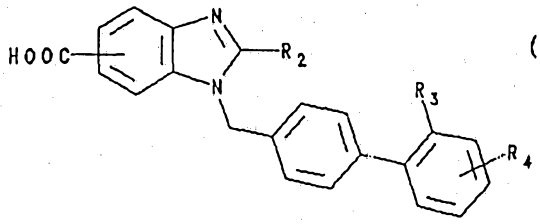
e) (to prepare a compound of formula I wherein R_3 represents a 1H-tetrazolyl group) reacting a compound of formula VII



(VII)

(wherein
R_1, R_2 and R_4 are as hereinbefore defined) with hydrazoic acid or a salt thereof;

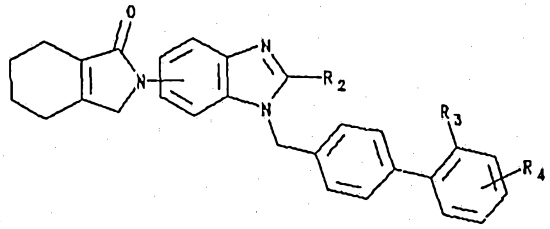
f) (to prepare compounds of formula I wherein R_1 represents a pentamethylene-oxazolin-2-yl group) reacting a compound of formula VIII



(VIII)

(wherein
R_2, R_3 and R_4 are as hereinbefore defined) with 1-aminomethyl-cyclohexanol in the presence of an acid-activating agent;

g) (to prepare a compound of formula I wherein R_1 represents a 2-oxo-3,4-tetramethylene-pyrrolidin-1-yl group) hydrogenating a compound of formula IX



(IX)

(wherein
R_2, R_3 and R_4 are as hereinbefore defined);

h) (to prepare compounds of formula I wherein R_1 represents an amino group substituted by a bicyclohexylcarbonyl or biphenylcarbonyl group, which

may additionally be substituted at the N-atom by a C_{1-3}-alkyl group, an aminocarbonylamino group substituted by a bicyclohexyl or biphenyl group and optionally additionally substituted by one or two C_{1-3}alkyl groups at the N-atom, a maleic acid amido or maleic acid imido group optionally mono- or disubstituted by substituents selected from C_{1-3}-alkyl and phenyl groups, a (C_{1-3}-alkyl)amino or phenyl(C_{1-3}-alkyl)amino group substituted by a C_{4-6}-alkylsulphonyl group or by a phenyl(C_{1-3}-alkyl)sulphonyl group, an amino or C_{1-3}-alkylamino group substituted by a naphthalenesulphonyl group and optionally substituted in the naphthalene ring by a di(C_{1-3}-alkyl)amino group or by one or two C_{1-3}-alkoxy groups, a 7-nitro-benzofurazan-4-yl-amino(C_{2-3}-alkanoyl)amino group, a benzofurancarbonyl-amino or 7-nitro-benzofurazan-4-yl-amino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent an amino group substituted by a phenylsulphonyl, cyclohexylmethylamino-carbonyl, 2-carboxycyclohexylmethylcarbonyl, 2-tert.-butoxycarbonyl-cyclohexylmethylcarbonyl, 2-carboxy-3,4,5,6-tetrahydrobenzoyl, N-methyl-phenylaminocarbonyl or 3-cyclohexylpropyl group, a methylamino group substituted by a propylsulphonyl, phenylsulphonyl, methylphenylsulphonyl or chlorophenylsulphonyl group, an n-pentylamino group substituted by a phenylsulphonyl or methoxyphenylsulphonyl group, an n-propylamino group substituted by a methylphenylsulphonyl or methoxyphenyl-sulphonyl group, an isopropylamino group substituted by a benzoyl or chlorophenylsulphonyl group, an N-acetyl-cyclohexylmethylamino, 3,4,5,6-tetrahydrophthalimido, hexahydrohomophthalimido, N-methanesulphonyl-2-phenylethylamino or N-chlorophenylsulphonyl-benzylamino group, and

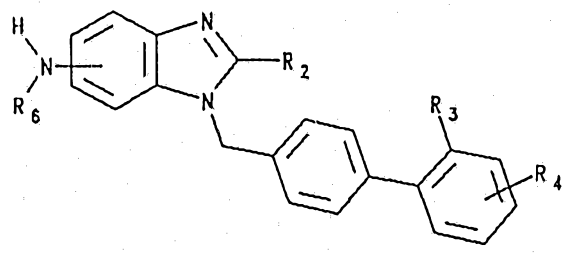
where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent a 2-oxo-1,2-dihydro-3,4-tetramethylene-pyrrolidin-1-yl group, and

where R_3 represents a carboxy group and R_2 represents a methyl, ethyl, n-propyl, n-butyl or methylmercapto group, R_1 in the 6-position may also represent a pyrrolidino-carbonylamino group, and

where R_3 represents a tetrazolyl group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent an n-pentylamino group substituted by a methylamino-carbonyl or cyclohexylaminocarbonyl group and R_1 in the 6-position may also represent a 3,3-dimethyl-glutaric acid imido or 4,4-tetramethylene-glutaric acid imido group, and

where R_3 represents a tetrazolyl group and R_2 represents an ethyl or n-propyl group, R_1 in the 6-position may also represent an N-benzenesulphonyl-methylamino group, and

where R_3 represents a tert.-butoxycarbonyl group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent a 2-carboxy-cyclohexylmethylcarbonylamino or pyrrolidinocarbonylamino group) reacting a compound of formula X



(X)

(wherein

R_2, R_3 and R_4 are as hereinbefore defined; and
R_6 represents a hydrogen atom, an n-pentyl, cyclohexylmethyl, C_{1-3}-alkyl or phenyl(C_{1-3}-alkyl) group) with a compound of formula XI

$$Z_4 - W - R_7 \qquad (XI)$$

(wherein
Z_4 represents a nucleophilic leaving group;
W represents a -CO- or $-SO_2-$ group; and
R_7 represents a 2-hydroxycarbonyl-ethenyl group wherein the ethenyl moiety is mono- or disubstituted by substituents selected from C_{1-3}-alkyl and phenyl groups, a C_{3-6}-alkyl group, a phenyl(C_{1-3}-alkyl) group, a naphthalene group optionally substituted by a di(C_{1-3}-alkyl)amino group or by one or two C_{1-3}-alkoxy groups, a methyl, phenyl, methylphenyl, methoxyphenyl, chlorophenyl, biphenyl, bicyclohexyl, 2-carboxy-cyclohexylmethyl, 2-carboxy-3,4,5,6-tetrahydrophenyl, 3-carboxy-1,1-dimethyl-propyl, 3-carboxy-2,2-tetramethylenepropyl, 7-nitro-benzofurazan-4-yl-aminomethyl or 7-nitro-benzofurazan-4-yl-aminoethyl group, and

where W represents a -CO- group, R_7 may also represent an R_8NR_9 group wherein

R_8 represents a hydrogen atom or a C_{1-3}-alkyl group,

R_9 represents a methyl, cyclohexyl, cyclohexylmethyl, phenyl, biphenyl or bicyclohexyl group, or

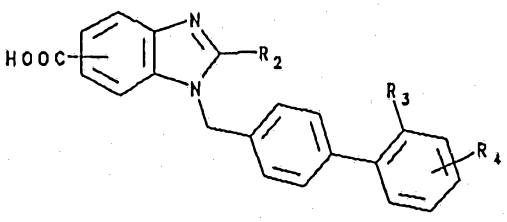
R_8 and R_9 together with the nitrogen atom between them represent a pyrrolidiro group, or

Z_4 together with R_9 represents another carbon-

nitrogen bond, and

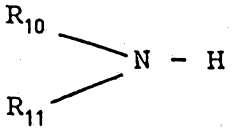
R_7 together with W may also represent a 7-nitro-benzofurazan-4-yl-amino group) or a reactive derivative of a carboxylic acid of formula XI;

i) (to prepare compounds of formula I wherein R_1 represents a tetrahydrobenzimidazolyl or imidazopyridinyl group, or a benzimidazolyl group optionally substituted in the phenyl nucleus by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group, by a C_{1-3}-alkoxy group or by a trifluoromethyl group, and in which the NH-group of the above-mentioned imidazole rings may additionally be substituted by a C_{1-6}-alkyl group or by a C_{3-7}-cycloalkyl group, a hydroxy(C_{5-7}-cycloalkyl)aminocarbonyl group, which may additionally be substituted at the N-atom by a C_{1-3}-alkyl group, or a straight-chained or branched hydroxy(C_{4-6}-alkyl)aminocarbonyl group) reacting a compound of formula XII



(XII)

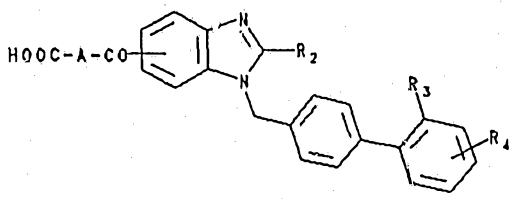
(wherein
R_2, R_3 and R_4 are as hereinbefore defined) or a reactive derivative thereof, for example an acid halide, ester, amide, anhydride or nitrile, with an amine of formula XIII



(XIII)

(wherein
R_{10} represents a hydrogen atom, a cycloalkyl group or a C_{1-6}-alkyl group; and
R_{11} represents a C_{4-6}-hydroxyalkyl group, a C_{5-7}-hydroxycycloalkyl group or a 2-aminophenyl group which may be substituted in the phenyl nucleus by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group, by a C_{1-3}-alkoxy group or by a trifluoromethyl group, a 2-aminocyclohexyl or 2-aminopyridyl group) optionally with simultaneous decarboxylation;

j) (to prepare compounds of formula I wherein R_1 represents a dihydro-pyridazin-3-one or a pyridazin-3-one group which may be substituted in the 2-position by an optionally phenyl-substituted C_{1-3}-alkyl group or at a carbon atom by one or two C_{1-3}-alkyl groups) reacting a carboxylic acid of formula XIV



(XIV)

(wherein
R_1, R_2, R_3 and R_4 are as hereinbefore defined; and
A represents an ethylene or ethenylene group optionally substituted by one or two C_{1-3}-alkyl groups) or a reactive acid derivative thereof, for example an ester, amide or halide thereof, with a hydrazine of formula XV

$$H_2N - NHR_{12} \qquad (XV)$$

(wherein
R_{12} represents a hydrogen atom or an optionally phenyl-substituted C_{1-3}-alkyl group);

k) resolving a 1-,3- isomer mixture of a compound of formula I by isomer separation into the 1- and 3-isomers thereof;

l) converting a compound of formula I into an addition salt thereof, more particularly, for pharmaceutical use into a physiologically acceptable salt thereof with an organic or inorganic acid or base or converting a salt of a compound of formula I into the free compound; and

m) carrying out a reaction according to any one of steps (a) to (l) above in which one or more groups are protected by a protecting group and subsequently removing any protecting group used.

In the reactions described above, any reactive groups present such as hydroxy, amino or alkylamino groups may optionally be protected during the reaction by conventional protecting groups which are split off again after the reaction.

Examples of suitable protecting groups for a hydroxy group are trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.-butyl, benzyl or tetrahydropyranyl groups and suitable protecting groups for an amino, alkylamino or imino group include acetyl, benzoyl, ethoxycarbonyl and benzyl groups.

The optional subsequent cleaving of a protecting group is preferably carried out by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as hydrochloric or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide, conveniently at temperatures between 0 and 100°C, preferably at the boiling temperature of the reaction mixture. However, a

benzyl group is preferably removed by hydrogenolysis, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid, conveniently at temperatures between 0 and 50°C, but preferably at ambient temperature, under a hydrogen pressure of 1 to 7 bar, preferably 3 to 5 bar.

The cyclisation of step (a) may conveniently be carried out in a solvent or mixture of solvents such as ethanol, isopropanol, glacial acetic acid, benzene, chlorobenzene, toluene, xylene, glycol, glycolmonomethylether, diethyleneglycol-dimethylether, sulpholane, dimethylformamide, tetraline or in an excess of the acylating agent used to prepare the compound of formula II, e.g. in the corresponding nitrile, anhydride, acid halide, ester or amide. The reaction is conveniently effected at temperatures between 0 and 250°C, preferably at the boiling temperature of the reaction mixture, optionally in the presence of a condensing agent such as phosphorusoxychloride, thionylchloride, sulphurylchloride, sulphuric acid, p-toluenesulphonic acid, methanesulphonic acid, hydrochloric acid, phosphoric acid, polyphosphoric acid or acetic anhydride, or optionally in the presence of a base such as potassium ethoxide or potassium tert.-butoxide. However, cyclisation may also be carried out without a solvent and/or condensing agent.

It is particularly advantageous to carry out the reaction of step (a) by preparing a compound of formula II in the reaction mixture by reducing a corresponding o-nitro-amino compound, optionally in the presence of a carboxylic acid of general formula R_2COOH, or by acylating a corresponding o-diamino compound. When the

reduction of the nitro group is broken off at the hydroxylamine stage, the N-oxide of a compound of formula I is obtained in the subsequent cyclisation. The resulting N-oxide is then converted by reduction into a corresponding compound of formula I. The subsequent reduction of the N-oxide of formula I obtained is preferably carried out in a solvent such as water, water/ethanol, methanol, glacial acetic acid, ethyl acetate or dimethylformamide, with hydrogen in the presence of a hydrogenation catalyst such as Raney nickel, platinum or palladium/charcoal, with metals such as iron, tin or zinc in the presence of an acid such as acetic, hydrochloric or sulphuric acid, with salts such as iron(II)sulphate, tin(II)chloride or sodium dithionite, or with hydrazine in the presence of Raney nickel at temperatures between 0 and 50°C, preferably at ambient temperature.

The reaction of step (b) may conveniently be carried out in a solvent or mixture of solvents such as methylene chloride, diethylether, tetrahydrofuran, dioxane, dimethyl-sulphoxide, dimethylformamide or benzene, optionally in the presence of an acid binding agent such as sodium carbonate, potassium carbonate, sodium hydroxide, potassium tert.-butoxide, triethylamine or pyridine, whilst the latter two may simultaneously also be used as solvent, conveniently at temperatures between 0 and 100°C, preferably at temperatures between ambient temperature and 50°C. A mixture of the 1- and 3-isomers is preferably obtained.

In step (c) functional derivatives of the carboxy group such as optionally substituted amides, esters, thiolesters, orthoesters, iminoethers, amidines and anhydrides, and nitrile and tetrazolyl groups may be converted by hydrolysis into a carboxy group, esters with tertiary alcohols, e.g. tert.butylesters, may be

converted by thermolysis into a carboxy group and esters with aralkanols, e.g. benzyl esters, may be converted by hydrogenolysis into a carboxy group.

The hydrolysis of step (c) is conveniently carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric, trichloroacetic or trifluoroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxane at temperatures between -10°C and 120°C, preferably at temperatures between ambient temperature and the boiling temperature of the reaction mixture. When hydrolysis is carried out in the presence of an organic acid such as trichloroacetic or trifluoroacetic acid, any alcoholic hydroxy groups present may simultaneously be converted into a corresponding acyloxy group such as a trifluoroacetoxy group.

If R_3' in a compound of formula V represents a cyano or aminocarbonyl group, such a group may also be converted into a carboxy group with a nitrite, e.g. sodium nitrite, in the presence of an acid such as sulphuric acid, which may simultaneously also be used as solvent, at temperatures between 0 and 50°C.

If R_3' in a compound of formula V represents for example a tert.-butyloxycarbonyl group, the tert.-butyl group may also be thermally cleaved, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic amount of an acid such as p-toluenesulphonic, sulphuric, phosphoric or polyphosphoric acid, conveniently at temperatures between 40°C and 100°C, preferably at the boiling temperature of the solvent used.

If R_3' in a compound of formula V represents for example a benzyloxycarbonyl group, the benzyl group may also be hydrogenolytically cleaved in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, more preferably at ambient temperature, under a hydrogen pressure of 1 to 5 bar. During hydrogenolysis, other groups may be reduced at the same time, e.g. a nitro group may be reduced to the amino group, a benzyloxy group to the hydroxy group, a vinylidene group to the corresponding alkylidene group or a cinnamic acid group to the corresponding phenylpropionic acid group, or they may be replaced by hydrogen atoms, e.g. a halogen may be replaced by a hydrogen atom.

If R_1 in a compound of formula V represents one of the above mentioned hydrolysable groups, it may be converted during the reaction into a corresponding carboxy or amino compound.

Suitable protecting groups for use in step (d) include, for example, triphenylmethyl, tributyl tin and triphenyl tin groups.

The cleaving of a protecting group is preferably carried out in the presence of a hydrohalic acid, more preferably in the presence of hydrochloric acid, in the presence of a base such as sodium hydroxide or alcoholic ammonia in a suitable solvent such as methylene chloride, methanol, methanol/ammonia, ethanol or isopropanol, conveniently at temperatures between 0 and 100°C, preferably at ambient temperature or, if the reaction is carried out in the presence of alcoholic ammonia, at elevated temperatures, e.g. at temperatures between 100 and

150°C, preferably at temperatures between 120 and 140°C.

The reaction of step (e) is preferably carried out in a solvent such as benzene, toluene or dimethylformamide at temperatures between 80 and 150°C, preferably at 125°C. Appropriately, either the hydrazoic acid is liberated during the reaction from an alkali metal azide, e.g. sodium azide in the presence of a weak acid such as ammonium chloride, or the tetrazolide salt obtained in the reaction mixture from the reaction with a salt of hydrazoic acid, preferably with aluminium azide or tributyl tin azide, which is also preferably produced in the reaction mixture by reacting aluminium chloride or tributyl tin chloride with an alkali metal azide such as sodium azide, is subsequently liberated by acidification with a dilute acid such as 2N hydrochloric or 2N sulphuric acid.

The reaction of step (f) is preferably carried out in a solvent such as tetrahydrofuran or dioxane in the presence of an acid activating agent such as carbonylimidazole at temperatures between 0 and 50°C, preferably at ambient temperature.

The catalytic hydrogenation of step (g) is conveniently carried out with hydrogen in the presence of a catalyst such as palladium/charcoal, in a solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid at temperatures between 0 and 50°C, preferably at ambient temperature, under a hydrogen pressure of 1 to 7 bar, preferably 3 to 5 bar.

Examples of nucleophilic leaving groups for Z_4 in step (h) include chlorine or bromine atoms, alkoxy or phenylalkoxy groups such as methoxy, ethoxy or benzyloxy groups or, if R_7 represents a hydrocarbon group, a hydroxy group.

The reaction of step (h) may conveniently be carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile or dimethylformamide, optionally in the presence of an acid activating agent or a dehydrating agent, e.g. in the presence of ethyl chloroformate, thionyl chloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, or an agent which activates the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine, which may simultaneously be used as solvents, conveniently at temperatures between -25 and 150°C, preferably at temperatures between -10°C and the boiling temperature of the solvent used.

If Z_4 represents a hydroxy group, however, it is particularly advantageous to carry out the reaction of step (h) with the reactive derivatives of a carboxylic acid of general formula XI, e.g. with the esters, thioesters, halides, anhydrides or imidazolides.

The reaction of step (i) may conveniently be carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile or dimethylformamide, optionally in the presence of an acid activating agent or a dehydrating agent, e.g. in the presence of ethyl chloroformate, thionyl chloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, or an agent

which activates the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine, which may simultaneously be used as solvents, conveniently at temperatures between -25 and 150°C, but preferably at temperatures between -10°C and the boiling temperature of the solvent used.

An ortho-benzamido compound optionally obtained in this way can then, if necessary, be converted into the desired benzimidazole compound by heating, preferably in a solvent or mixture of solvents such as ethanol, isopropanol, glacial acetic acid, benzene, chlorobenzene, toluene, xylene, glycol, glycol-monomethylether, diethyleneglycol-dimethylether, sulpholane, dimethylformamide or tetraline, optionally in the presence of a condensing agent such as phosphorus oxychloride, thionyl chloride, sulphuryl chloride, sulphuric acid, p-toluenesulphonic acid, methanesulphonic acid, hydrochloric acid, phosphoric acid, polyphosphoric acid, acetic acid anhydride or optionally in the presence of a base such as potassium ethoxide or potassium tert.-butoxide. However, this cyclisation may also be carried out without a solvent and/or condensing agent.

The reaction of step (j) may conveniently be carried out in a solvent such as methanol, ethanol, isopropanol, glacial acetic acid or propionic acid and/or in an excess of the hydrazine or hydrazine hydrate used, at temperatures between 0 and 200°C, preferably at temperatures between 20 and 150°C, more preferably at the boiling temperature of the reaction mixture, and optionally in the presence of an acid such as sulphuric or p-toluenesulphonic acid as a condensing agent. The reaction may, however, also be carried out without a

solvent.

The isomer separation of step (k) is preferably carried out by chromatography using a substrate such as silica gel or aluminium oxide.

The compounds of formula I obtained may, if desired, be converted into the acid addition salts thereof, more particularly for pharmaceutical use the physiologically acceptable salts thereof with inorganic or organic acids. Suitable acids for this purpose include hydrochloric, hydrobromic, sulphuric, phosphoric, fumaric, succinic, lactic, citric, tartaric and maleic acid.

Furthermore, the new compounds of formula I thus obtained, if they contain a carboxy or 1H-tetrazolyl group, may, if desired, subsequently be converted into the salts thereof with inorganic or organic bases, more particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

Some of the compounds of general formulae II to XV used as starting materials are known from the literature. Otherwise these compounds may be obtained by methods known from the literature.

Thus, for example, a compound of general formula II may be obtained by alkylation of a corresponding o-amino-nitro compound and subsequent reduction of the nitro group.

Compounds of general formulae III, V, VI, VII, VIII, IX, X, XII or XIV used as starting materials may be obtained

by alkylation of a corresponding o-phenylenediamine or a corresponding o-amino-nitro compound, followed by reduction of the nitro group and subsequent cyclisation of an o-diamino-phenyl compound thus obtained, optionally followed by cleaving any protecting group used or by NH-alkylation of a corresponding 1H-benzimidazole, whilst the isomer mixture thus obtained may subsequently be resolved by conventional methods, e.g. chromatography. Some of the starting compounds mentioned above are described in EP-A-392317.

The new compounds of general formula I and the physiologically acceptable salts thereof have valuable pharmacological properties. They are angiotensin antagonists, in particular, angiotensin-II-antagonists.

Thus in a further aspect the present invention provides a pharmaceutical composition comprising a compound of formula I or a physiologically acceptable salt thereof together with at least one pharmaceutical carrier or excipient.

In a still further aspect the present invention provides the use of a compound of formula I or a physiologically acceptable salt thereof for the manufacture of a therapeutic agent for the treatment of hypertension, cardiac insufficiency, ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), for the prevention of cardiac insufficiency progression after myocardial infarct, or for the treatment of diabetic nephropathy, glaucoma, gastrointestinal diseases and bladder diseases.

In a still yet further aspect the present invention provides a method of treatment of the human or non-human animal body to combat hypertension, cardiac insufficiency, ischaemic peripheral circulatory

disorders, myocardial ischaemia (angina), cardiac insufficiency progression following myocardial infarction, diabetic nephropathy, glaucoma, gastrointestinal diseases and bladder diseases, said method comprising administering to said body a compound of formula I or a physiologically acceptable salt thereof.

By way of example, the following compounds:

A = 4'-[[2-n-propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid;

B = 4'-[[2-n-butyl-6-(3,4,5,6-tetrahydro-phthalimino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-dihydrate;

C = 4'-[[2-n-butyl-6-(2,3-diphenyl-maleic acid imido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid;

D = 4'-[[2-n-butyl-6-(2,3-dimethyl-maleic acid imido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid;

E = 4'-[[2-n-butyl-6-(N-phenylmethanesulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid;

F = 4'-[[2-n-butyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

G = 4'-[[2-n-butyl-6-(2-oxo-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

H = 4'-[[2-n-butyl-6-(2-oxo-hexamethyleneimino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-

biphenyl;

I = 4'-[[2-n-butyl-6-(3,3-dimethylglutarimido)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

J = 4'-[[2-n-butyl-6-(N-methylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

K = 4'-[[2-n-butyl-6-(cyclohexylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl hydrate; and

L = 4'-[[2-n-butyl-6-(2-oxo-3,4-tetramethylene-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

were tested for their biological effects as follows:

Rats (male, 180-220 g) are anaesthetised with sodium hexobarbital (150 mg/kg i.p.). After they have become unconscious, a tracheal cannula is inserted, the animals are pithed and then immediately artificially respirated with a ventilator pump. The arterial blood pressure is recorded by means of a cannula in the carotid artery using a Bell & Howell pressure recorder. The substances are administered in the jugular vein through a cannula.

Test substances are administered in three doses (10, 20 and 30 mg/kg i.v.), with one dose of substance being tested on each animal. Three minutes after the intravenous administration of the test substance, angiotensin-II is administered intravenously in increasing doses and in this way a cumulative dose-activity relationship is achieved for angiotensin-II in the presence of the test substances. The increase in

arterial blood pressure is measured.

These dose-activity curves are compared with standard curves for angiotensin-II without the use of any test substances. Using a computer program, the shift to the right in the dose-activity curves for angiotensin-II as a result of the administration of the test substances are determined and corresponding pA_2-values are calculated for the test substances.

The pA_2 values of the above-mentioned test compounds A to L are between 6.0 and 7.5.

Moreover, when the above-mentioned compounds were administered in a dose of 30 mg/kg i.v. no toxic side effects, e.g. negative inotropic effects or heart rhythm disorders, were observed. Accordingly, the compounds are well tolerated.

The new compounds and their physiologically acceptable salts are suitable for the treatment of hypertension and cardiac insufficiency and also for treating ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), for the prevention of the progression of cardiac insufficiency after myocardial infarct and for treating diabetic nephropathy, glaucoma, gastrointestinal diseases and bladder diseases.

The new compounds and the physiologically acceptable salts thereof are also suitable for treating pulmonary diseases, e.g. lung oedema and chronic bronchitis, for preventing arterial re-stenosis after angioplasty, for preventing thickening of blood vessel walls after vascular operations, and for preventing arteriosclerosis and diabetic angiopathy. In view of the effects of angiotensin on the release of acetyl choline and dopamine in the brain, the new angiotensin antagonists

are also suitable for alleviating central nervous system disorders, e.g. depression, Alzheimer's disease, Parkinson syndrome, bulimia and disorders of cognitive function.

The dosage required to achieve these effects is conveniently, when administered intravenously, 20 to 100 mg, preferably 30 to 70 mg, and, when administered orally, 50 to 200 mg, preferably 75 to 150 mg, 1 to 3 times a day. For this purpose, the compounds of formula I and salts thereof, optionally in conjunction with other active substances such as antihypertensives, diuretics and/or calcium channel blockers, may be incorporated together with one or more inert conventional carriers and/or diluents, for example with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propylene-glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

Suitable active ingredients for the above-mentioned combinations include for example atenolol, bendroflumethiazide, chlorothiazide, (di)hydralazine hydrochloride, hydrochlorothiazide, metoprolol, prazosin, propranolol, spironolactone, benzthiazide, cyclothiazide, ethacrinic acid, furosemide, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine and nitrendipine. The individual dosages for these ingredients can range from about one-fifth of the usually minimal recommended dosage up to the maximum recommended dosage, for example from 15 to 200 mg of

hydrochlorothiazide, from 125 to 2000 mg of chlorothiazide, from 15 to 200 mg of ethacrinic acid, from 5 to 80 mg of furosemide, from 20 to 480 mg of propranolol, from 5 to 60 mg of felodipine, from 5 to 60 mg of nifedipine or from 5 to 60 mg of nitrendipine.

The following non-limiting Examples are provided to illustrate the invention. Unless otherwise specified all percentages and ratios given are by weight:

Example 1

4'-[[2-n-Propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid and 4'-[[2-n-Propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

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a) Methyl-2-n-propyl-benzimidazole-5-carboxylate

A solution of 23.9 g (100 mMol) of methyl 3,4-diamino-benzoate dihydrochloride and 11.7 g (110 mMol) of butyric acid chloride in 100 ml of phosphorus oxychloride is refluxed for 2 hours. Then about 80 ml of phosphorus oxychloride are distilled off and the residue is mixed with about 150 ml of water. The oily crude product precipitated is extracted three times with 50 ml of ethyl acetate and after evaporation purified by column chromatography (600 g of silica gel; eluant: methylene chloride/methanol (30:1 by volume)).
Yield: 15.0 g of oil (69% of theory)

b) 2-n-Propyl-benzimidazole-5-carboxylic acid-hemisulphate

A solution of 15.0 g (73 mMol) of methyl 2-n-propyl-benzimidazole-5-carboxylate and 8 g (200 mMol) of sodium hydroxide in 200 ml of water and 400 ml of ethanol is refluxed for 2 hours. Then the alcohol is distilled off, the aqueous solution is acidified with dilute sulphuric acid (pH 4-5) and evaporated using a rotary evaporator. The product crystallising out is suction filtered, washed with 50 ml of acetone and 50 ml of diethylether and dried.
Yield: 9.1 g (61% of theory),
Melting point: > 220°C.
$C_{11}H_{12}N_2O_2 \times 1/2\ H_2SO_4$ (253.26)
Calculated: C 52.17 H 5.17 N 11.06 S 6.33

Found:	51.87	5.23	11.11	6.41

c) 2-n-Propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazole

A solution of 6.7 g (25 mMol) of 2-n-propyl-benzimidazole-5-carboxylic acid-hemisulphate and 4.9 g (25 mMol) of 2-methylaminoaniline-dihydrochloride in 200 g of polyphosphoric acid is stirred for 5 hours at 150°C, then poured onto 600 ml of water and made alkaline with concentrated ammonia whilst cooling with ice. The resulting solution is extracted three times with 200 ml of ethyl acetate, the crude product thus obtained is purified by column chromatography (300 g of silica gel; eluant: methylene chloride/methanol = 15:1 by volume).

Yield: 2.8 g of oil (39% of theory),

$C_{18}H_{18}N_4$ (290.37)

Calculated:	C 74.46	H 6.25	N 9.29
Found:	73.92	6.32	18.96

d) Tert.-butyl 4'-[[2-n-propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid and
tert.-butyl 4'-[[2-n-propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

A solution of 2.0 g (6.9 mMol) of 2-n-propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazole and 0.91 g (7.5 mMol) of potassium tert.-butoxide in 50 ml of dimethylsulphoxide is stirred for 90 minutes at ambient temperature, then 2.6 g (7.5 mMol) of tert.-butyl 4'-bromomethyl-biphenyl-2-carboxylate are added and the mixture is stirred for a further 15 hours at ambient temperature. The mixture is then poured onto 300 ml of water and extracted three times with 50 ml of ethyl acetate. The crude product obtained after evaporation

of the organic phase is purified by column chromatography (300 g silica gel; eluant: methylene chloride/methanol = 30:1 by volume). In this way, 2.7 g (70% of theory) of an isomer mixture are obtained, which when analysed by NMR spectroscopy, contains about 1.18 g of tert.-butyl 4'-[(2-n-propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate and about 1.52 g of tert.-butyl 4'-[(2-n-propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate.

R_f value: 0.43 (methylene chloride/methanol = 19:1 by volume)

e) 4'-[[2-n-Propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid and
4'-[[2-n-propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

2.70 g of the isomer mixture obtained in Example 1d are dissolved in 100 ml of methylene chloride, mixed with 40 ml of trifluoroacetic acid and stirred for 4 hours at ambient temperature. The mixture is then evaporated to dryness in vacuo, the residue is dissolved in 100 ml of 2N sodium hydroxide solution, the solution is washed with 50 ml of diethylether and the product mixture is precipitated by acidifying the aqueous phase with acetic acid. By column chromatography (400 g of silica gel, eluant: methylene chloride/methanol = 15:1 by volume) of the solid thus obtained, 0.7 g (58% of theory) of 4'-[[2-n-propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]-biphenyl-2-carboxylate are obtained, melting point 219-220°C

$C_{32}H_{28}N_4O_2$ (500.60)

Calculated:	C 76.78	H 5.64	N 11.19
Found:	76.54	5.57	11.01

R_f value: 0.15 (methylene chloride/methanol = 9:1 by volume)

and 0.9 g (74% of theory) of 4'-[[2-n-propyl-6-(1-

methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate are obtained, melting point 217-218°C

$C_{32}H_{28}N_4O_2$ (500.60)

Calculated: C 76.78 H 5.64 N 11.19

Found: 76.63 5.55 11.29

R_f value: 0.40 (methylene chloride/methanol = 9:1)

The following compounds are obtained analogously:

4'-[[2-n-propyl-6-(1,6-dimethyl-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-butyl-6-(1-methyl-5-bromo-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-butyl-6-(1-methyl-5-methoxy-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-butyl-6-(1-n-butyl-5-trifluoromethyl-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-butyl-6-(1-n-hexyl-5-methyl-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(1-methyl-5-chloro-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Example 2

4'-[[2-n-Butyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 43% of theory,
Melting point: amorphous
$C_{33}H_{30}N_4O_2$ (514.60)

	C	H	N
Calculated:	77.02	5.88	10.89
Found:	76.88	5.83	10.55

R_f value: 0.42 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Mass spectrum: $(M + H)^+ = 515$

Example 3

4'-[[6-(Biphenyl-4-carbonylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid x 0.25 H_2O

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(biphenyl-4-carbonylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 70.6% of theory,
Melting point: 316-317°C
$C_{38}H_{33}N_3O_3$ x 0.25 H_2O (584.20)

	C	H	N
Calculated:	78.13	5.78	7.19
Found:	78.12	5.79	7.08

R_f value: 0.25 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 4

4'-[[6-(Biphenylyl-4-aminocarbonylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid trifluoroacetate-semihydrate

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(biphenylyl-4-aminocarbonylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 97.0% of theory,
Melting point: 171-172°C
$C_{38}H_{34}N_4O_3 \times CF_3COOH \times 1/2\ H_2O$ (717.74)
Calculated: C 66.94 H 5.06 N 7.81
Found: 67.13 4.99 7.76
R_f value: 0.25 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 5

4'-[(6-Benzenesulphonamido-2-n-butyl-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[(6-benzenesulphonamido-2-n-butyl-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 75.0% of theory,
Melting point: 251-252°C
$C_{31}H_{29}N_3O_4S$ (539.65)
Calculated: C 69.00 H 5.42 N 7.79 S 5.94
Found: 68.96 5.52 7.82 5.86
R_f value: 0.50 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 50:45:5)

Example 6

4'-[[6-(N-Benzenesulphonyl-methylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(N-benzenesulphonyl-methylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 70.0% of theory,
Melting point: 211-212°C
$C_{32}H_{31}N_3O_4S$ (553.68)

	C	H	N	S
Calculated:	69.42	5.64	7.59	5.79
Found:	69.24	5.66	7.53	6.02

R_f value: 0.55 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 7

4'-[[2-n-Butyl-6-(cyclohexylmethylaminocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-trifluoroacetate

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(cyclohexylmethylaminocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 91.1% of theory,
Melting point: 149-150°C
$C_{33}H_{38}N_4O_3 \times CF_3COOH$ (652.71)

	C	H	N
Calculated:	64.41P	6.02	8.58
Found:	64.23	6.09	8.73

R_f value: 0.25 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 8

4'-[[2-n-Butyl-6-(N-cyclohexylmethyl-acetamido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-cyclohexylmethyl-acetamido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 78.6% of theory,
Melting point: 185-187°C
$C_{34}H_{39}N_3O_3$ (537.70)

	C	H	N
Calculated:	75.95	7.31	7.81
Found:	75.75	7.40	7.65

R_f value: 0.45 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 9

4'-[[6-(Bicyclohexyl-4-carbonylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(bicyclohexyl-4-carbonylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 93.3% of theory,
Melting point: 104-106°C
$C_{38}H_{45}N_3O_3 \times CF_3COOH$ (705.82)

	C	H	N
Calculated:	68.07	6.57	5.95
Found:	68.38	6.64	5.80

R_f value: 0.30 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 10

4'-[[6-(Bicyclohexyl-4-aminocarbonylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid semitrifluoroacetate-monohydrate

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(bicyclohexyl-4-aminocarbonylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 94.9% of theory,
Melting point: 119-120°C
$C_{38}H_{46}N_4O_3 \times 1/2\ CF_3COOH \times H_2O$ (681.83)

Calculated:	C 68.70	H 7.17	N 8.22
Found:	68.32	6.91	7.81

R_f value: 0.30 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 11

4'-[[2-n-Butyl-6-(3,4,5,6-tetrahydro-phthalimino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid dihydrate

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(3,4,5,6-tetrahydro-phthalimino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 14.7% of theory,
Melting point: 119-122°C
$C_{33}H_{31}N_3O_4 \times 2\ H_2O$ (533.63)

Calculated:	C 69.58	H 6.19	N 7.38
Found:	69.77	6.34	7.65

R_f value: 0.45 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 12

4'-[[2-n-Butyl-6-(5-dimethylamino-naphthalen-1-sulphonamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-semitrifluoroacetate

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(5-dimethylamino-naphthalen-1-sulphonamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.

Yield: 92.3% of theory,

Melting point: 148-150°C

$C_{37}H_{36}N_4O_4S \times 1/2\ CF_3COOH$ (689.78)

Calculated:	C 66.17	H 5.33	N 8.12	S 4.64
Found:	65.40	5.33	7.92	5.19

Example 13

4'-[[2-n-Butyl-6-(2,3-diphenyl-maleic acid imido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(2,3-diphenyl-maleic acid imido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.

Yield: 82.6% of theory,

Melting point: 236-237°C

$C_{41}H_{33}N_3O_4$ (631.73)

Calculated:	C 77.95	H 5.27	N 6.65
Found:	77.66	5.24	6.56

R_f value: 0.65 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 14

4'-[[2-n-Butyl-6-(N-methanesulphonyl-2-phenylethyl-amino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-methanesulphonyl-2-phenylethylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 71.4% of theory,
Melting point: 215-216°C
$C_{34}H_{35}N_3O_4$ (581.73)

Calculated:	C	70.20	H	6.06	N	7.22	S 5.51
Found:		69.99		6.14		7.23	5.55

R_f value: 0.25 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 15

4'-[[2-n-Butyl-6-(2,3-dimethyl-maleic acid imido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(2,3-dimethyl-maleic acid imido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 69.6% of theory,
Melting point: 289-290°C
$C_{31}H_{29}N_3O_4$ (507.59)

Calculated:	C	73.35	H	5.76	N	8.28	
Found:		73.14		5.90		8.20	

R_f value: 0.55 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 16

4'-[[6-(N-Benzenesulphonyl-n-pentylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(N-benzenesulphonyl-n-pentylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 83.9% of theory,
Melting point: 243-244°C
$C_{36}H_{39}N_3O_4S$ (609.78)

Calculated:	C	70.91	H	6.45	N	6.89	S 5.26
Found:		70.92		6.21		6.98	5.19

R_f value: 0.45 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 17

4'-[[2-n-Butyl-6-(N-4-methoxybenzenesulphonyl-n-pentylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-4-methoxybenzenesulphonyl-n-pentylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 84.6% of theory,
Melting point: 207-208°C
$C_{37}H_{41}N_3O_5S$ (639.81)

Calculated:	C	69.46	H	6.46	N	6.57	S 5.01
Found:		69.31		6.50		6.77	5.21

R_f value: 0.50 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 18

4'-[[2-n-Butyl-6-(N-4-chlorobenzenesulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-4-chlorobenzenesulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 84.8 % of theory,
Melting point: 240-241°C

$C_{32}H_{30}ClN_3O_4S$ (588.12)

Calculated:	C	65.35	H	5.14	N	7.14	Cl	6.03	S 5.45
Found:		65.02		5.30		7.17		6.21	5.46

Example 19

4'-[[2-n-Butyl-6-(N-phenylmethanesulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-phenylmethanesulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 54.9% of theory,
Melting point: 208-209°C

$C_{33}H_{33}N_3O_4S$ (567.70)

Calculated:	C	69.82	H	5.86	N	7.40	S 5.65
Found:		69.54		5.79		7.47	5.59

Example 20

4'-[[2-n-Butyl-6-(N-4-methylbenzenesulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-4-methylbenzenesulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 92.5% of theory,
Melting point: 259-260°C
$C_{33}H_{33}N_3O_4S$ (567.70)

	C	H	N	S
Calculated:	69.82	5.86	7.40	5.65
Found:	69.70	5.90	7.44	5.68

R_f value: 0.25 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 21

4'-[[2-n-Butyl-6-(N-n-propylsulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-n-propylsulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 67.3% of theory,
Melting point: 222-223°C
$C_{29}H_{33}N_3O_4S$ (519.66)

	C	H	N	S
Calculated:	67.03	6.40	8.09	6.17
Found:	67.02	6.49	8.04	6.18

R_f value: 0.20 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 22

4'-[[2-n-Butyl-6-(N-4-methoxybenzenesulphonyl-n-propylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-4-methoxybenzenesulphonyl-n-propylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.

Yield: 86.4% of theory,

Melting point: 227-228°C

$C_{35}H_{37}N_3O_5S$ (611.75)

Calculated:	C 68.72	H 6.10	N 6.87	S 5.24
Found:	68.54	6.20	6.88	5.25

R_f value: 0.25 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 23

4'-[[2-n-Butyl-6-(N-4-methylbenzenesulphonyl-n-propylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-4-methylbenzenesulphonyl-n-propylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid and trifluoroacetic acid in methylene chloride.

Yield: 82.8% of theory,

Melting point: 223-224°C

$C_{35}H_{37}N_3O_4S$ (595.76)

Calculated:	C 70.56	H 6.26	N 7.05	S 5.38
Found:	70.25	6.20	7.24	5.61

R_f value: 0.28 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 24

4'-[[2-n-Butyl-6-(N-4-chlorobenzenesulphonyl-isopropylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-4-chlorobenzenesulphonyl-isopropylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 82.1% of theory,
Melting point: 260-261°C
$C_{34}H_{34}ClN_3O_4S$ (616.17)

Calculated:	C 66.28	H 5.56	N 6.82	Cl 5.75	S 5.20
Found:	66.05	5.77	7.05	5.87	5.34

R_f value: 0.30 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 25

4'-[[6-(N-Benzoyl-isopropylamino)-2-n-butyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(N-benzoyl-isopropylamino)-2-n-butyl-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 58.3% of theory,
Melting point: 209-210°C
$C_{35}H_{35}N_3O_3$ (545.68)

Calculated:	C 77.04	H 6.46	N 7.70
Found:	76.66	6.57	7.65

R_f value: 0.20 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 26

4'-[[2-n-Butyl-6-(1H,3H-quinazolin-2,4-dion-3-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid hemihydrate

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(1H,3H-quinazolin-2,4-dion-3-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 53.1% of theory,
Melting point: 338-340°C
$C_{33}H_{28}N_4O_4 \times 1/2\ H_2O$ (553.61)

Calculated:	C 71.59	H 5.28	N 10.12
Found:	71.19	5.33	10.22

Example 27

4'-[[2-n-Butyl-6-(N-4-chlorobenzenesulphonyl-benzylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

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Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-4-chlorobenzenesulphonyl-benzylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 64.5% of theory,
Melting point: 212-213°C
$C_{38}H_{34}ClN_3O_4S$ (664.22)

Calculated:	C 68.72	H 5.16	N 6.33	Cl 5.34	S 4.83
Found:	68.76	5.27	6.39	5.62	4.81

R_f value: 0.28 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 28

4'-[[2-n-Butyl-6-(N-n-butanesulphonyl-benzylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

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Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-n-butanesulphonyl-benzylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 66.4% of theory,
Melting point: 193-194°C
$C_{36}H_{39}N_3O_4S$ (609.78)

	C	H	N	S
Calculated:	70.91	6.45	6.89	5.26
Found:	70.76	6.54	6.94	5.40

R_f value: 0.25 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 29

4'-[[2-n-Butyl-6-(N-6,7-dimethoxynaphthalen-2-sulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

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Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(N-6,7-dimethoxynaphthalen-2-sulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 87.0% of theory,
Melting point: 261-262°C
$C_{38}H_{37}N_3O_6S$ (663.79)

	C	H	N	S
Calculated:	68.76	5.62	6.33	4.83
Found:	69.00	6.00	6.15	5.07

R_f value: 0.23 (silica gel; eluant: ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

Example 30

4'-[[2-n-Butyl-6-(2-oxo-3,4-tetramethylene-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(2-oxo-3,4-tetramethylene-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 38.0% of theory,
Melting point: 146-148°C
$C_{33}H_{33}N_3O_3$ (519.65)
R_f value: 0.30 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 31

4'-[[2-n-Butyl-5-(2-oxo-3,4-tetramethylene-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-5-(2-oxo-3,4-tetramethylene-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 15.5% of theory,
Melting point: amorphous
$C_{33}H_{33}N_3O_3$ (519.65)
R_f value: 0.20 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 32

4'-[[2-n-Butyl-6-(3,3-dimethylpiperidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(3,3-dimethylpiperidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 86% of theory,
Melting point: from 120°C (sintering)
$C_{32}H_{37}N_3O_2$ (495.70)

Calculated:	C	77.54	H	7.52	N 8.48
Found:		77.54		7.24	8.19

R_f value: 0.35 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 33

4'-[[2-n-Butyl-6-heptamethyleneimino-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-heptamethyleneimino-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylate and trifluoroacetic acid.
Yield: 71% of theory,
Melting point: 195-198°C
$C_{32}H_{37}N_3O_2$ (495.60)

Calculated:	C	77.55	H	7.52	N 8.48
Found:		77.40		7.66	8.23

R_f value: 0.40 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 34

4'-[[2-n-Butyl-6-(piperidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert-butyl 4'-[[2-n-butyl-6-(piperidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid.
Yield: 84% of theory,
Melting point: 199-200°C
$C_{30}H_{33}N_3O_2$ (467.60)
Calculated: C 77.06 H 7.11 N 8.99
Found: 76.85 7.28 9.02
R_f value: 0.40 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 35

4'-[[2-n-Butyl-6-(4-methylpiperidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(4-methyl-piperidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid.
Yield: 82% of theory,
Melting point: 162-165°C
$C_{31}H_{35}N_3O_2$ (481.60)
Calculated: C 77.31 H 7.33 N 8.73
Found: 77.20 7.19 8.63
R_f value: 0.40 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 36

4'-[[2-n-Butyl-6-hexamethyleneimino-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[(2-n-butyl-6-hexamethyleneimino-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid.
Yield: 34% of theory,
Melting point: 197-199°C
$C_{31}H_{35}N_3O_2$ (481.60)
Calculated: C 77.31 H 7.33 N 8.73
Found: 76.99 7.35 8.62
R_f value: 0.40 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 37

4'-[[2-n-Propyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid.
Yield: 60% of theory,
Melting point: 208-210°C
$C_{29}H_{29}N_3O_3$ (467.60)
Calculated: C 74.49 H 6.25 N 8.99
Found: 74.00 6.29 8.90
R_f value: 0.50 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 38

4'-[[2-n-Propyl-6-(propanesultam-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(propanesultam-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid.
Yield: 49% of theory,
Melting point: amorphous
$C_{27}H_{27}N_3O_4S$ (489.58)

Calculated:	C 66.23	H 5.56	N 8.56	S 6.55
Found:	66.08	5.50	8.37	6.51

R_f value: 0.47 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Mass spectrum: $(M + H)^+ = 490$

Example 39

4'-[[2-n-Propyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid.
Yield: 57% of theory,
Melting point: amorphous
$C_{28}H_{29}N_3O_4S$ (503.63)

Calculated:	C 66.77	H 5.80	N 8.34	S 6.37
Found:	66.59	5.77	8.18	6.33

R_f value: 0.51 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Mass spectrum: $(M + H)^+ = 504$

Example 40

4'-[[2-n-Butyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid.
Yield: 51% of theory,
Melting point: 203-205°C
$C_{29}H_{31}N_3O_4S$ (517.63)

Calculated:	C 67.29	H 6.04	N 8.12	S 6.19
Found:	67.22	5.97	7.97	6.10

R_f value: 0.52 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Mass spectrum: $(M + H)^+ = 518$

Example 41

4'-[[2-n-Butyl-6-(benzoxazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

a) 2-n-Butyl-5-(benzoxazol-2-yl)-benzimidazole

1.43 g (12 mMol) of thionyl chloride are added dropwise at 10°C with stirring to a suspension of 2.52 g (10 mMol) of 2-n-butyl-benzimidazole-5-carboxylic acid in 15 ml of N-methylpyrrolidinone. The mixture is stirred for a further 15 minutes at ambient temperature, then 1.31 g (11 mMol) of 2-aminophenol are added and the mixture is heated to 140°C for 2 hours. The mixture is then poured onto about 50 g of ice and 5 ml of 30% sodium hydroxide solution are added with stirring. The crude product precipitated is suction filtered and purified by column chromatography (300 g of silica gel; eluant: methylene chloride + 3% ethanol).

Yield: 1.2 g (41% of theory),
Melting point: 118-120°C
$C_{18}H_{17}N_3O$ (291.36)

Calculated:	C 74.20	H 5.88	N 14.42
Found:	73.98	5.97	14.20

b) Isomer mixture of
4'-[[2-n-butyl-6-(benzoxazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid nitrile and
4'-[[2-n-butyl-5-(benzoxazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid nitrile

A solution of 1 g (3.43 mMol) of 2-n-butyl-5-(benzoxazol-2-yl)-benzimidazole and 0.98 g (3.60 mMol) of 4'-bromomethyl-biphenyl-2-carboxylic acid nitrile in 20 ml dimethylsulphoxide is mixed with 0.41 g (3.6 mMol) of potassium tert.-butoxide and stirred for 48 hours at ambient temperature. The mixture is then poured onto 100 ml of water, saturated with sodium chloride and extracted three times with 30 ml of ethyl acetate. By column chromatography (200 g of silica gel; eluant: ethyl acetate/petroleum ether (1:1 by volume)) 1.4 g (85% of theory) of a mixture of the isomers is obtained in the ratio 1:1 and this mixture begins to sinter from 130°C.

$C_{32}H_{26}N_4O$ (482.59)

Calculated:	C 79.64	H 5.43	N 11.61
Found:	79.64	5.36	11.59

c) 4'-[[2-n-Butyl-6-(benzoxazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

A solution of the (1:1) isomer mixture of 4'-[[2-n-butyl-6-(benzoxazol-2-yl)-benzimidazol-1-yl]methyl]-biphenyl-2-carboxylic acid nitrile and 4'-[[2-n-butyl-5-(benzoxazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid nitrile in 20 ml of dimethylformamide is mixed with 2 g of ammonium chloride and 2 g of sodium azide and heated to 120-130°C for 4 hours. After a further 2 g of ammonium chloride and 2 g of sodium azide have been added and the mixture has been heated to

120-130°C for a further 18 hours, it is poured onto 100 ml of water. The product mixture precipitated is suction filtered and separated by column chromatography (300 g of silica gel, eluant: methylene chloride + 3% ethanol).

Yield: 100 mg (20% of theory) in amorphous form.

$C_{32}H_{27}N_7O$ (525.62)

Calculated: C 73.12 H 5.18 N 18.66

Found: 73.10 5.50 18.42

R_f value: 0.75 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

The following compounds are obtained analogously to Example 41:

4'-[[2-n-butyl-6-(4,5-dihydro-2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(4,5-dihydro-2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-ethyl-6-(4,5-dihydro-2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-butyl-6-(2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-ethyl-6-(2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(2-methyl-4,5-dihydro-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(2-benzyl-4,5-dihydro-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-

biphenyl

4'-[[2-n-butyl-6-(1-methyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(1-n-hexyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-butyl-6-(1-n-butyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(1-cyclopropyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(1-cyclohexyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(1-methyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-butyl-6-(1-methyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(1-n-propyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(1-n-hexyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-butyl-6-(1-n-butyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(1-cyclopropyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-6-(1-cyclohexyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Example 42

4'-[[2-n-Propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl and

4'-[[2-n-propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

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Prepared analogously to Example 41 from a mixture of 4'-[[2-n-propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and 4'-[[2-n-propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.

5-isomer:
Yield: 29% of theory,
Melting point: amorphous
$C_{32}H_{28}N_8$ (524.61)

	C	H	N
Calculated:	73.26	5.38	21.36
Found:	73.03	5.22	21.26

Mass spectrum: $(M + H)^+ = 525$

6-isomer:
Yield: 34% of theory,
Melting point: 198-200°C
$C_{32}H_{28}N_8$ (524.61)

	C	H	N
Calculated:	73.26	5.38	21.36
Found:	73.11	5.27	21.19

Mass spectrum: $(M + H)^+ = 525$

Example 43

4'-[[2-n-Butyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-n-butyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 28% of theory,
Melting point: 224-226°C
$C_{33}H_{30}N_8$ (538.63)
Calculated: C 73.58 H 5.61 N 20.81
Found: 73.31 5.73 19.99
R_f value: 0.76 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Mass spectrum: $(M + H)^+ = 539$

Example 44

4'-[[2-n-Butyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-n-butyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 20% of theory,
Melting point: amorphous
$C_{30}H_{31}N_7O$ (505.63)
Calculated: C 67.94 H 6.23 N 17.33
Found: 67.67 6.13 17.52
R_f value: 0.30 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 45

4'-[[2-n-Butyl-6-(3,3-dimethylpiperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-n-butyl-6-(3,3-dimethylpiperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 8% of theory,
Melting point: sintering from 148°C
$C_{32}H_{37}N_7 \times HCl$ (519.70)
Mass spectrum: $(M + H)^+ = 520$

Example 46

4'-[[2-n-Butyl-6-(4,4-tetramethyleneglutarimido)-benzimidazol-1-yl]-methyl]-4-chloro-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-n-butyl-6-(4,4-tetramethyleneglutarimido)-benzimidazol-1-yl]-methyl]-4-chloro-biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 40% of theory,
Melting point: sintering from 160°C
$C_{34}H_{34}N_7O_2Cl$ (608.16)

Calculated:	C 67.15	H 5.64	N 16.12
Found:	66.90	5.86	15.86

R_f value: 0.50 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 47

4'-[[2-n-Butyl-6-(propanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-n-butyl-6-(propanesultam-1-yl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and

dimethylformamide.
Yield: 46% of theory,
Melting point: 203-205°C
$C_{28}H_{29}N_7O_2S$ (527.70)
Calculated: C 63.73 H 5.54 N 18.58 S 6.08
Found: 62.52 5.56 18.40 6.00
R_f value: 0.35 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 48

4'-[[2-n-Butyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-n-butyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 30% of theory,
Melting point: 189-191°C
$C_{29}H_{31}N_7O_2S$ (541.70)
Calculated: C 64.30 H 5.95 N 18.10 S 5.92
Found: 64.40 5.75 17.90 5.85
R_f value: 0.37 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 49

4'-[[2-n-Propyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-n-propyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 37% of theory,
Melting point: 204-206°C
$C_{28}H_{29}N_7O_2S$ (527.63)
Calculated: C 63.73 H 5.54 N 18.58 S 6.08

Found: 63.70 5.49 18.37 6.19
R_f value: 0.36 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Mass spectrum: m/e = 527

Example 50

Mixture of
4'-[[2-n-butyl-6-(2-hydroxy-cyclohexylaminocarbonyl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl
and
4'-[[2-n-butyl-5-(2-hydroxy-cyclohexylaminocarbonyl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

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Prepared analogously to Example 41 from a mixture of 4'-[[2-n-butyl-6-(2-hydroxy-cyclohexylaminocarbonyl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and 4'-[[2-n-butyl-5-(2-hydroxy-cyclohexylamino-carbonyl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 8% of theory,
Melting point: 198-200°C
$C_{32}H_{35}N_7O_2$ (549.70)
R_f value: 0.30 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Mass spectrum: $(M + H)^+ = 550$

Example 51

4'-[[2-n-Butyl-6-(2-oxo-pyrrolidin-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

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Prepared analogously to Example 41 from 4'-[[2-n-butyl-6-(2-oxo-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]-biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 15% of theory,
Melting point: 153-155°C

$C_{29}H_{29}N_7O$ (491.60)
Calculated: C 70.85 H 5.95 N 19.95
Found: 70.79 6.17 19.71
R_f value: 0.45 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Mass spectrum: $(M + H)^+ = 492$

Example 52

Mixture of
4'-[[2-n-butyl-6-(1,1-dimethyl-2-hydroxy-ethylamino-carbonyl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl and
4'-[[2-n-butyl-5-(1,1-dimethyl-2-hydroxy-ethylamino-carbonyl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 41 from a mixture of 4'-[[2-n-butyl-6-(1,1-dimethyl-2-hydroxy-ethylamino-carbonyl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and 4'-[[2-n-butyl-5-(1,1-dimethyl-2-hydroxy-ethylamino-carbonyl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 14% of theory,
Melting point: amorphous
$C_{30}H_{33}N_7O_2$ (523.60)
R_f value: 0.30 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Mass spectrum: $(M + H)^+ = 524$

Example 53

4'-[[2-n-Butyl-6-(2-oxo-hexamethyleneimino)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-n-butyl-6-(2-oxo-hexamethyleneimino)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 34% of theory,
Melting point: amorphous
$C_{31}H_{33}N_7O$ (519.70)
Calculated: C 71.65 H 6.40 N 18.87
Found: 70.99 6.32 18.75
R_f value: 0.15 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 54

4'-[[2-n-Propyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-n-propyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 14.5% of theory,
Melting point: sintering from 125°C
$C_{29}H_{29}N_7O$ (491.60)
R_f value: 0.25 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Mass spectrum: $(M + H)^+ = 492$

Example 55

4'-[[2-n-Butyl-6-(3,3-dimethylglutarimido)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

a) 4'[[2-n-Butyl-6-(3,3-dimethylglutarimido)-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl

1.8 g (3.3 mMol) of 4'-bromomethyl-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl are added to a solution of 1.04 g (3.3 mMol) of 2-n-butyl-5-(3,3-dimethyl-glutarimido)-benzimidazole and 425 mg (3.8 mMol) of potassium tert.-butoxide in 25 ml of dimethylsulphoxide. The mixture is stirred for 3 hours at ambient temperature, then stirred into 150 ml of water, extracted three times with 30 ml of ethyl acetate, then the organic extracts are dried and concentrated by evaporation. The residue obtained is purified by column chromatography (300 g of silica gel; eluant: ethyl acetate/petroleum ether (2:1 by volume)).
Yield: 400 mg (15% of theory),
R_f value: 0.38 (ethyl acetate/petroleum ether = 6:1)

b) 4'-[[2-n-Butyl-6-(3,3-dimethylglutarimido)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

A solution of 400 mg (0.5 mMol) of 4'-[[2-n-butyl-6-(3,3-dimethylglutarimido)-benzimidazol-1-yl]-methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl in 10 ml of methanol is mixed with 1.5 ml of methanolic hydrochloric acid and stirred for 2 hours at ambient temperature, then concentrated by evaporation, the residue is mixed with 15 ml of water and made alkaline with concentrated ammonia, whereupon the product goes into solution. By acidification with glacial acetic acid, the crude product is precipitated and then purified by column chromatography (150 g of silica gel; eluant: methylene

chloride + 5% ethanol).
Yield: 150 mg (55% of theory),
Melting point: 184-186°C
$C_{32}H_{33}N_7O_2$ (547.70)
Calculated: C 70.18 H 6.07 N 17.90
Found: 69.98 6.20 17.67

Example 56

4'-[[2-n-Butyl-6-(N-methylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 55 from 4'-[[2-n-butyl-6-(N-methylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and hydrochloric acid in ethanol.
Yield: 53.8% of theory,
Melting point: 124-126°C
$C_{33}H_{38}N_8O$ (550.71)
R_f value: 0.25 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)
Calculated: C 69.79 H 6.95 N 20.35
Found: 69.78 7.05 20.31
Mass spectrum: $(M + H)^+ = 492$

Example 57

4'-[[2-n-Butyl-5-(N-methylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl-dihydrate

---

Prepared analogously to Example 55 from 4'-[[2-n-butyl-5-(N-methylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and hydrochloric acid in ethanol.
Yield: 76.2% of theory,
Melting point: 201-203°C
$C_{32}H_{38}N_8O \times 2\ H_2O$ (586.74)

Calculated: C 65.50 H 7.21 N 19.09
Found: 65.43 7.07 19.12

Example 58

4'-[[2-n-Butyl-6-(N-cyclohexylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl-hydrate

---

Prepared analogously to Example 55 from 4'-[[2-n-butyl-6-(N-cyclohexylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and hydrochloric acid in ethanol.
Yield: 95.2% of theory,
Melting point: 128-132°C
$C_{37}H_{46}N_8O \times H_2O$ (636.84)
Calculated: C 69.78 H 7.59 N 17.59
Found: 69.61 7.71 17.41
R_f value: 0.45 (silica gel; eluant: ethanol/ammonia = 80:40:2 by volume)

Example 59

4'-[[2-n-Butyl-5-(N-cyclohexylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl-hydrate

---

Prepared analogously to Example 55 from 4'-[[2-n-butyl-5-(N-cyclohexylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and hydrochloric acid in ethanol.
Yield: 88.6% of theory,
Melting point: 117-120°C
$C_{37}H_{46}N_8O \times H_2O$ (636.84)
Calculated: C 69.78 H 7.59 N 17.59
Found: 70.06 7.58 17.56
R_f value: 0.45 (silica gel; eluant: ethanol/ammonia = 80:40:2 by volume)

Example 60

4'-[[2-n-Butyl-6-(5-dimethylaminonaphthalen-1-sulphonamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl-hydrate

---

Prepared analogously to Example 55 from 4'-[[2-n-butyl-6-(5-dimethylaminonaphthalen-1-sulphonamino)-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and hydrochloric acid in ethanol.
Yield: 44.7% of theory,
$C_{37}H_{36}N_8O_2S \times H_2O$ (674.81)

Calculated:	C	65.85	H	5.67	N	16.60	S 4.75
Found:		65.80		5.46		16.42	4.90

Example 61

4'-[[2-n-Butyl-6-(2-oxo-3,4-tetramethylene-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

420 mg (0.81 mMol) of 4'-[[2-n-butyl-6-(2-oxo-1,2-dihydro-3,4-tetramethylene-pyrrol-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid are dissolved in 60 ml of methanol and 60 ml of ethyl acetate and hydrogenated with the addition of 200 mg of palladium on charcoal (10%) under 5 bar of hydrogen pressure and at 40°C. The catalyst is removed by suction filtering, the solvent is evaporated off and the crude product is purified by column chromatography (200 g of silica gel; eluant: methylene chloride + 3% ethanol).
Yield: 260 mg (62% of theory),
Melting point: amorphous
$C_{33}H_{35}N_3O_3$ (521.67)

Calculated:	C	75.98	H	6.76	N	8.06
Found:		75.75		6.62		8.24

Example 62

Mixture of
4'-[[2-n-butyl-6-(5,5-pentamethylene-oxazolin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl
and
4'-[[2-n-butyl-5-(5,5-pentamethylene-oxazolin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

A solution of 930 mg (2 mMol) of an isomer mixture of 4'-[[2-n-butyl-6-carboxy-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl and 4'-[[2-n-butyl-5-carboxy-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl and 356 mg (2.2 mMol) of carbonyldiimidazole in 30 ml of tetrahydrofuran is stirred for 30 minutes at ambient temperature. Then 332 mg (2 mMol) of 1-(aminomethyl)-cyclohexanol-dihydrochloride are added and the mixture is stirred for a further 15 hours at ambient temperature. The mixture is then concentrated by evaporation, 2 ml of thionyl chloride are slowly added dropwise, the mixture is stirred for one hour, the thionyl chloride is distilled off and the residue is mixed with 5 ml of ice water. The insoluble crude product is purified by column chromatography (150 g of silica gel; eluant: methylene chloride + 5% ethanol). In this way, 25 mg (2% of theory) of a mixture of 4'-[[2-n-butyl-6-(5,5-pentamethylene-oxazolin-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl
and
4'-[[2-n-butyl-5-(5,5-pentamethylene-oxazolin-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl
is obtained.

Melting point: from 215°C (decomp.)

$C_{33}H_{35}N_7O$ (545.67)

Mass spectrum: $(M + H)^+ = 546$

Example 63

4'-[[2-n-Butyl-6-(N-methyl-phenylaminocarbonylamino)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid

A solution of 0.8 g (2.00 mMol) of 4'-[[2-n-butyl-6-aminobenzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid and 0.9 g of N-methyl-isatoic acid anhydride in 3 ml of pyridine is refluxed for 48 hours, then evaporated to dryness, the residue is suspended in about 5 ml of methylene chloride, suction filtered, washed with a further 5 ml of methylene chloride and dried.
Yield: 0.66 g (62% of theory),
Melting point: 274-276°C

$C_{33}H_{32}N_4O_3$ (532.60)

Calculated:	C 74.41	H 6.06	N 10.57
Found:	74.23	5.94	10.66

Example 64

4'-[[2-n-Butyl-5-(3-carboxy-propionyl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylic acid

A solution of 200 mg (0.39 mMol) of methyl 4'-[[2-n-butyl-5-(3-methoxycarbonyl-propionyl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylate and 0.75 ml of sodium hydroxide solution in 4 ml of ethanol is stirred for 2 hours at 75°C, then mixed with 40 ml of water and acidified with glacial acetic acid. The alcohol is then distilled off, the resulting mixture is stirred for one hour at ambient temperature, the product precipitated is suction filtered, washed with 10 ml of water and dried.
Yield: 120 mg (64% of theory),
Melting point: 200-202°C

$C_{29}H_{28}N_2O_4$ (484.60)

Calculated:	C 71.88	H 5.83	N 5.78
Found:	71.66	5.86	5.63

Example 65

4'-[[2-n-Butyl-6-(3-carboxy-2-methyl-propionyl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid x 0.25 H_2O

Prepared analogously to Example 64 from methyl 4'-[[2-n-butyl-6-(3-methoxycarbonyl-2-methyl-propionyl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and sodium hydroxide solution in ethanol.
Yield: 18% of theory,
Melting point: 193-194°C
$C_{30}H_{30}N_2O_5$ x 1/4 H_2O (498.60)

Calculated:	C 71.62	H 6.11	N 5.56
Found:	71.72	6.09	5.68

R_f value: 0.37 (silica gel; eluant: methylene chloride/ethanol/glacial acetic acid = 18:1:0.05 by volume)

Example 66

4'-[[2-n-Butyl-6-(3-carboxy-propionyl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 64 from methyl 4'-[[2-n-butyl-6-(3-methoxycarbonyl-propionyl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and sodium hydroxide solution in ethanol.
Yield: 97% of theory,
Melting point: 240-242°C
$C_{29}H_{28}N_2O_5$ (484.60)

Calculated:	C 71.88	H 5.83	N 5.78
Found:	71.74	6.07	5.93

Example 67

4'-[[2-n-Butyl-6-(2,3-dimethylmaleic acid imino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

52.5 mg (0.1 mMol) of 4'-[[2-n-butyl-6-(2,3-dimethylmaleic acid amino)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate are heated to boiling for one hour in 2 ml of bis-(2-methoxy-ethyl)-ether. The solvent is removed by distillation and the oily residue is distributed in ethyl acetate/water. The organic phase is washed twice more with water, dried with magnesium sulphate and concentrated by rotary evaporation. The residue is triturated in 1 ml of acetone, suction filtered, washed with ether and dried in vacuo at 75°C.

Yield: 29.0 mg (57.2% of theory),

Melting point: 289-291°C

$C_{31}H_{29}N_3O_4$ (507.59)

Calculated:	C 73.35	H 5.76	N 8.29
Found:	73.50	5.64	8.10

Example 68

4'-[[2-n-Butyl-6-(3,4,5,6-tetrahydro-phthalimino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-hydrate

---

0.275 g (0.5 mMol) of 4'-[[2-n-butyl-6-(2-carboxy-3,4,5,6-tetrahydrobenzamino)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylate are refluxed for 4 hours in 5 ml of pyridine. The mixture is evaporated to dryness in vacuo by rotary evaporation and the crude product is recrystallised from acetone. It is suction filtered, washed with acetone and dried in vacuo at 70°C.

Yield: 0.2 g (72.4% of theory),

Melting point: 226-228°C

$C_{30}H_{31}N_3O_4 \times H_2O$ (551.64)
Calculated: C 71.85 H 6.03 N 7.62
Found: 71.83 5.90 7.61

Example 69

Tert.-butyl 4'-[[2-n-butyl-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate

---

2.0 g (15 mMol) of pyrrolidinocarbonyl chloride are placed in 50 ml of dry chloroform and 2.3 g (6 mMol) of tert.-butyl 4'-[(6-amino-2-n-butyl-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate dissolved in 50 ml of dry pyridine are added dropwise for one hour. The reaction solution is stirred for a further 24 hours and then concentrated by rotary evaporation. The oily residue is distributed in ethyl acetate and 10% sodium hydrogen carbonate solution, the organic phase is separated off and, after drying with magnesium sulphate, concentrated by rotary evaporation. Purification is carried out using a silica gel column (particle size: 0.063 - 0.2 mm), eluting with petroleum ether/ethyl acetate = 3:7. The corresponding column fractions are concentrated by rotary evaporation and dried in vacuo at 50°C.
Yield: 1.7 g (61.8% of theory),
Melting point: 68-70°C (amorphous)
$C_{34}H_{40}N_4O_3$ (552.72)
R_f value: 0.35 (silica gel; eluant: ethyl acetate/ethanol = 19:1 by volume)

Example 70

4'-[[2-n-Butyl-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid trifluoroacetate-monohydrate

---

Prepared analogously to Example 1 from tert.-butyl 4'-

[[2-n-butyl-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid/methylene chloride.
Yield: 91.7% of theory,
Melting point: 233-234°C
$C_{30}H_{32}N_4O_3 \times CF_3COOH \times H_2O$ (628.25)

Calculated:	C 61.14	H 5.61	N 8.91
Found:	61.25	5.62	9.09

R_f value: 0.48 (silica gel; eluant: ethyl acetate:ethanol:ammonia = 50:45:5 by volume)

Example 71

4'-[[2-n-Butyl-6-(2,3-dimethylmaleic acid imino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

314 mg (0.5 mMol) of 4'-[(6-amino-2-n-butyl-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acid trifluoroacetate are refluxed together with 76 mg (0.6 mMol) of 2,3-dimethylmaleic acid anhydride in 10 ml of pyridine for 18 hours. The solvent is then removed by rotary evaporation and the oily substance is distributed in ethyl acetate and 10% sodium hydrogen carbonate solution. The organic phase is separated off, dried with magnesium sulphate and concentrated by rotary evaporation after being filtered. By trituration with acetone and ether, a white crystalline product is obtained which is dried at 50°C *in vacuo* after suction filtering.
Yield: 165 mg (65.0% of theory),
Melting point: 288-290°C
$C_{31}H_{29}N_3O_4$ (507.59)

Calculated:	C 73.35	H 5.76	N 8.29
Found:	73.14	5.94	8.32

Example 72

4'-[(2-n-Butyl-6-hexahydrohomophthalimino-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 71 from 4'-[(6-amino-2-n-butyl-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acid and hexahydrohomophthalic acid anhydride in pyridine.
Yield: 15.3% of theory,
Melting point: 183-185°C
$C_{34}H_{35}N_3O_4$ (549.67)

Calculated:	C 74.29	H 6.49	N 7.64
Found:	74.09	6.47	7.80

Example 73

4'-[[2-n-Butyl-6-(benzofuran-2-carbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 71 from 4'-[(6-amino-2-n-butyl-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acid and benzofuran-2-carboxylic acid anhydride in pyridine.
Yield: 80.7% of theory,
Melting point: 321-323°C
$C_{34}H_{39}N_3O_4$ (543.62)

Calculated:	C 75.12	H 5.38	N 7.73
Found:	74.92	5.45	7.87

Example 74

4'-[[2-n-Butyl-6-(3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon-1-yl)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene

chloride.
Yield: 42.2% of theory,
Melting point: 119-122°C
$C_{36}H_{36}N_4O_3 \times H_2O$ (590.72)

Calculated:	C	73.20	H	6.48	N 9.48
Found:		73.11		6.50	9.67

Example 75

4'-[[2-n-Butyl-6-(2-carboxy-cyclohexylmethylcarbonyl-amino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid hydrate

a) Tert.-butyl 4'-[[2-n-butyl-6-(2-carboxy-cyclohexylmethylcarbonylamino)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylate

1.3 g (2.86 mMol) of tert.-butyl 4'-[(6-amino-2-n-butyl-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate, 0.6 g (5.35 mMol) of hexahydrohomophthalic acid anhydride and 5 ml of pyridine are refluxed with stirring for 3 hours. Then the pyridine is removed by rotary evaporation in vacuo, the residue is crystallised from acetone, washed with acetone and dried in vacuo at 70°C.
Yield: 0.67 g (37.6% of theory),
Melting point: 227-229°C
$C_{38}H_{45}N_3O_5$ (623.79)

Calculated:	C	73.17	H	7.27	N 6.74
Found:		72.93		7.15	6.94

b) 4'-[[2-n-butyl-6-(2-carboxy-cyclohexylmethylcarbonyl-amino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

0.6 g (0.06 mMol) of tert.-butyl 4'-[[2-n-butyl-6-(2-carboxy-cyclohexylmethylcarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate, 30 ml of methylene chloride and 10 ml of trifluoroacetic acid are stirred for 3 hours at ambient temperature. The mixture is diluted with 20 ml of methylene chloride, extracted with

water, the organic phase is dried over sodium sulphate and evaporated to dryness. The residue is dissolved in ethanol and made alkaline by the addition of ammonia. The solvent is distilled off in vacuo. The remaining aqueous solution is acidified with acetic acid, the product which crystallises out is suction filtered, washed with water and dried in vacuo at 70°C.
Yield: 0.55 g (98.2% of theory),
Melting point: 160-162°C
$C_{34}H_{37}N_3O_5 \times H_2O$ (585.68)

Calculated:	C 69.72	H 6.71	N 7.17
Found:	69.63	6.64	7.33

Example 76

4'-[[2-n-Butyl-6-(2-carboxy-3,4,5,6-tetrahydro-benzamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

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0.4 g (1 mMol) of 4'-[(6-amino-2-n-butyl-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acid, dissolved in 7 ml of pyridine, are mixed with 0.34 g (1.1 mMol) of 1-cyclohexene-1,2-dicarboxylic acid anhydride at ambient temperature and stirred for 2½ hours. The mixture is cooled with ice and the product which crystallises out is suction filtered, washed with cooled acetone and dried in vacuo at 70°C.
Yield: 0.37 g (67.2% of theory),
Melting point: 250-252°C
$C_{33}H_{33}N_3O_5$ (551.64)

Calculated:	C 71.85	H 6.03	N 7.62
Found:	71.70	5.99	7.60

Example 77

4'-[[2-n-Propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

604 mg (1.0 mMol) of tert.-butyl 4'-[[2-nitro-5-(1-methylbenzimidazol-2-yl)-N-n-butyryl-anilino]methyl]-biphenyl-2-carboxylate are stirred in 50 ml of methylene chloride with the addition of 10 ml of trifluoroacetic acid at ambient temperature for 3 hours. The solvent is then distilled off, the residue is dissolved in 25 ml of glacial acetic acid and hydrogenated at 80°C with the addition of 500 mg of 10% palladium/charcoal. In order to work up the product, the solvent is distilled off in vacuo, the residue is dissolved in 30 ml of 2N sodium hydroxide solution and the solution is washed with 20 ml of diethyl ether. The crude product precipitated by the acidification of the aqueous phase is purified by subsequent column chromatography (80 g silica gel, eluant: methylene chloride/methanol = 15:1 by volume).
Yield: 90 mg (18% of theory),
Melting point: 214-216°C
$C_{32}H_{28}N_4O_2$ (500.60)

Calculated:	C 76.78	H 5.64	N 11.19
Found:	76.58	5.49	11.30

Example 78

4'-[[2-n-Propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

A suspension of 940 mg (2.0 mMol) of tert.-butyl 4'-[(2-n-propyl-6-carboxy-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate and 320 mg (2.0 mMol) of carbonyldiimidazole in a solution of 1.0 ml of triethylamine in 30 ml of tetrahydrofuran is stirred for 30 minutes at ambient temperature, then 250 mg (2.0 mMol) of 2-methylamino-aniline are added and the mixture is stirred for a

further 16 hours. It is then evaporated to dryness and the residue is refluxed in 20 ml of phosphorus oxychloride, with stirring, for 1 hour. The majority of the phosphorus oxychloride is then distilled off, the dark, greasy residue is decomposed with 30 ml of water, the strongly acidic suspension thus obtained is refluxed for about 1 hour, adjusted to pH 6 after cooling and then concentrated by evaporation. The crude product obtained is purified by column chromatography (120 g of silica gel, eluant: methylene chloride/methanol = 15:1 by volume).

Yield: 73 mg (7.3% of theory),

Melting point: 213-215°C

$C_{32}H_{28}N_4O_2$ (500.60)

Calculated:	C 76.78	H 5.64	N 11.19
Found:	76.61	5.64	10.94

Example 79

4'-[[2-n-Propyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

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Within 10 minutes, 155 mg (1.0 mMol) of 5-chloro-valeric acid chloride, dissolved in 5 ml of tetrahydrofuran, are added dropwise to a solution of 650 mg (1.0 mMol) of 4'-[(2-n-propyl-6-amino-benzimidazol-1-yl)-methyl]-2-(1H-triphenylmethyl-tetrazol-5-yl)-biphenyl in 30 ml of tetrahydrofuran and the mixture is stirred for a further hour at ambient temperature, then evaporated to dryness. The residue is stirred into 20 ml of ethanol, then a solution of 2.0 mMol of sodium ethoxide in 20 ml of ethanol is added and the resulting mixture is refluxed for one hour. After cooling, 10 ml of methanolic hydrochloric acid are added dropwise, the mixture is stirred for a further two hours at ambient temperature and then evaporated down. The residue is mixed with 10 ml of water and made alkaline with concentrated ammonia, whereupon the product goes into solution. By acidifying with glacial acetic acid the crude product is

precipitated and then purified by column chromatography (70 g silica gel, eluant: methylene chloride + 5% ethanol).
Yield: 54 mg (11% of theory),
Melting point: sintering from 117°C
$C_{29}H_{29}N_7O$ (491.60)

Calculated:	C 70.85	H 5.95	N 19.95
Found:	70.69	5.94	19.99

The following compounds are obtained analogously:

4'-[[2-n-butyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl
Yield: 16% of theory,
Melting point: amorphous
$C_{30}H_{31}N_7O$ (505.63)

Calculated:	C 67.94	H 6.23	N 17.33
Found:	67.81	6.29	17.18

4'-[[2-n-butyl-6-(2-oxo-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl
Yield: 9% of theory,
Melting point: 150-151°C
$C_{29}H_{29}N_7O$ (491.60)

Calculated:	C 70.85	H 5.95	N 19.95
Found:	70.61	6.08	19.80

Example 80

4'-[[2-n-Butyl-6-(propanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Within 10 minutes, a solution of 265 mg (1.5 mMol) of 3-chloro-propanesulphonic acid chloride in 5 ml of tetrahydrofuran is added dropwise to a solution of 665 mg (1.0 mMol) of 4'-[(2-n-butyl-6-aminobenzimidazol-1-yl)-methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and 1 ml of triethylamine in 30 ml of tetrahydrofuran and the mixture is stirred for 1½ hours

at ambient temperature. The mixture is then evaporated to dryness, the residue is taken up in 20 ml of ethanol, a solution of 3.0 mMol of sodium ethoxide in 20 ml of ethanol is added and the resulting mixture is refluxed for two hours. After cooling, 10 ml of methanolic hydrochloric acid are added dropwise, the mixture is stirred for a further two hours at ambient temperature and finally concentrated by evaporation. The residue is mixed with 10 ml of water and brought into solution with concentrated ammonia. By acidifying with glacial acetic acid, the crude product is precipitated and then purified by column chromatography (70 g of silica gel, eluant: methylene chloride + 5% ethanol).

Yield: 68.5 mg (13% of theory),

Melting point: 202-205°C

$C_{28}H_{29}N_7O_2S$ (527.70)

Calculated:	C	63.73	H	5.54	N 18.58
Found:		63.70		5.61	18.35

The following compounds are obtained analogously:

4'-[[2-n-butyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Yield: 10% of theory,

Melting point: 185-187°C

$C_{29}H_{31}N_7O_2S$ (541.70)

Calculated:	C	64.30	H	5.95	N 18.10
Found:		64.19		5.91	17.92

4'-[[2-n-propyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Yield: 17% of theory,

Melting point: 203-205°C

$C_{28}H_{29}N_7O_2S$ (527.63)

Calculated:	C	63.73	H	5.54	N 18.58
Found:		63.63		5.54	18.39

Example 81

4'-[[2-n-Butyl-6-(1-benzyl-imidazolidin-2,4-dion-3-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid trifluoroacetate

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(1-benzyl-imidazolidin-2,4-dion-3-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 58% of theory,
Melting point: amorphous
$C_{35}H_{32}N_4O_4 \times CF_3COOH$ (686.71)

Calculated:	C 64.72	H 4.84	N 8.16
Found:	64.48	4.68	8.09

Example 82

4'-[[2-n-Propyl-6-(5,5-pentamethylene-imidazolidin-2,4-dion-3-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(5,5-pentamethylene-imidazolidin-2,4-dion-3-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 27% of theory,
Melting point: amorphous
$C_{33}H_{34}N_4O_4$ (550.63)

Calculated:	C 71.98	H 6.22	N 10.18
Found:	71.93	6.16	10.09

R_f value: 0.60 (silica gel; eluant: methylene chloride/ethanol = 9:1 by volume)

Example 83

4'-[[2-Ethyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-ethyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]methyl]-biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 33% of theory,
Melting point: sintering from 150°C
$C_{28}H_{27}N_7O$ (477.58)

Calculated:	C 70.42	H 5.70	N 20.53
Found:	70.48	5.72	19.88

Example 84

4'-[[2-Ethyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-ethyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid nitrile and sodium azide in dimethylformamide.
Yield: 36% of theory,
Melting point: decomposition from 240°C
$C_{27}H_{27}N_7O_2S$ (513.64)

Calculated:	C 63.14	H 5.30	N 19.09
Found:	63.06	5.19	19.08

Example 85

4'-[[2-n-Propyl-6-(3-n-hexyl-imidazo[4,5-b]pyridin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(3-n-hexyl-imidazo[4,5-b]pyridin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and

trifluoroacetic acid in methylene chloride.
Yield: 57% of theory,
Melting point: amorphous
$C_{36}H_{37}N_5O_2$ (571.74)
Calculated: C 75.63 H 6.52 N 12.25
Found: 75.58 6.48 12.08

Example 86

4'-[[2-n-Propyl-6-(3-methyl-imidazo[4,5-b]pyridin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(3-methyl-imidazo[4,5-b]pyridin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 40% of theory,
Melting point: 208-210°C
$C_{31}H_{27}N_5O_2$ (501.60)
Calculated: C 74.23 H 5.43 N 13.96
Found: 74.19 5.32 13.94

Example 87

4'-[[2-n-Propyl-6-(1-methyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(1-methyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 53% of theory,
Melting point: amorphous
$C_{28}H_{28}N_4O_2$ (452.57)
Calculated: C 74.31 H 6.24 N 12.38
Found: 74.31 6.11 12.27

The following compounds are obtained analogously to Example 87:

4'-[[2-n-butyl-6-(1-methyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(1-n-hexyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-butyl-6-(1-n-butyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(1-cyclopropyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(1-cyclohexyl-imidazolin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(1-methyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-butyl-6-(1-methyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(1-n-hexyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-butyl-6-(1-n-butyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(1-cyclopropyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(1-cyclohexyl-imidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Example 88

4'-[[2-n-Propyl-6-(1,5-dimethyl-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(1,5-dimethyl-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 48% of theory,
Melting point: 256-258°C
$C_{33}H_{30}N_4O_2$ (514.63)

Calculated:	C 77.02	H 5.88	N 10.89
Found:	76.91	5.83	10.72

Example 89

4'-[[2-n-Propyl-6-(1-methyl-5-trifluoromethyl-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(1-methyl-5-trifluoromethyl-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 56% of theory,
Melting point: 183-186°C
$C_{33}H_{27}F_3N_4O_2$ (568.61)

Calculated:	C 69.71	H 4.79	N 9.85
Found:	69.58	4.72	9.80

Example 90

4'-[[2-n-Propyl-6-(5-methyl-imidazolidin-2,4-dion-3-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(5-methyl-imidazolidin-2,4-dion-3-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 29% of theory,
Melting point: amorphous
$C_{28}H_{26}N_4O_4$ (482.55)

Calculated:	C 69.69	H 5.43	N 11.61
Found:	69.67	5.40	11.55

Example 91

4'-[(2-n-Propyl-6-(1-methyl-imidazolidin-2,4-dion-3-yl)-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[(2-n-propyl-6-(1-methyl-imidazolidin-2,4-dion-3-yl)-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 32% of theory,
Melting point: amorphous
$C_{28}H_{26}N_4O_4$ (482.55)

Calculated:	C 69.69	H 5.43	N 11.61
Found:	69.61	5.38	11.49

Example 92

4'-[(2-n-Propyl-6-(1-butyl-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[(2-n-propyl-6-(1-butyl-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate and trifluoroacetic

acid in methylene chloride.
Yield: 59% of theory,
Melting point: sintering from 149°C

$C_{35}H_{34}N_4O_2$ (542.69)

Calculated:	C	77.46	H	6.32	N 10.32
Found:		77.37		6.31	10.35

Example 93

4'-[(2-n-Butyl-6-(1H-benzimidazol-2-yl)-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[(2-n-butyl-6-(1H-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 62% of theory,
Melting point: 200-202°C

$C_{32}H_{28}N_4O_2$ (500.61)

Calculated:	C	76.78	H	5.64	N 11.19
Found:		76.54		5.60	11.16

Example 94

4'-[(2-n-Butyl-6-hexahydrohomophthalimino-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid

---

0.4 g (0.64 mMol) of tert.-butyl 4'-[(2-n-butyl-6-(2-carboxy-cyclohexylmethylcarbonylamino)-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate are refluxed for 1½ hours with stirring in 5 ml of phosphorus oxychloride. After cooling, the mixture is poured onto ice water and the crude product precipitated is removed by suction filtering. This is dissolved in ethanol/water, made alkaline with ammonia and concentrated in vacuo until it crystallises out. It is then suction filtered, washed with water and dried in vacuo at 120°C.
Yield: 0.15 g (42.8% of theory),

Melting point: 241-243°C

$C_{34}H_{35}N_3O_4$ (549.66)

Calculated: C 74.29 H 6.49 N 7.64

Found: 74.14 6.64 7.81

Example 95

4'-[(2-n-Butyl-6-(7-nitro-benzofurazan-4-yl-amino)-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acid

Prepared from 4'-[(6-amino-2-n-butyl-benzimidazol-1-yl)methyl]biphenyl-2-carboxylic acid and 4-chloro-7-nitro-benzofurazan in pyridine at ambient temperature.

Yield: 13.1% of theory,

R_f value: 0.75 (silica gel, methylene chloride/ethanol = 9:1)

$C_{31}H_{26}N_6O_5$ (562.58)

Calculated: C 66.18 H 4.66 N 14.93

Found: 66.35 4.76 15.13

Example 96

4'-[[2-Ethyl-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-trifluoroacetate-semihydrate

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-ethyl-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.

Yield: 80.9% of theory,

Melting point: 178-179°C

$C_{28}H_{28}N_4O_3 \times CF_3COOH \times 0.5\ H_2O$ (591.59)

Calculated: C 60.90 H 5.11 N 9.47

Found: 61.10 5.22 9.26

R_f value: 0.48 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 97

4'-[[2-Methyl-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-trifluoroacetate

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-methyl-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 82.1% of theory,
Melting point: 181-182°C
$C_{27}H_{26}N_4O_3 \times CF_3COOH$ (568.55)
Calculated: C 61.26 H 4.79 N 9.85
Found: 60.99 5.09 9.89
R_f value: 0.38 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 98

4'-[[2-n-Propyl-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-trifluoroacetate

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-propyl-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 79.7% of theory,
Melting point: 207-208°C
$C_{29}H_{30}N_4O_3 \times CF_3COOH$ (596.61)
Calculated: C 62.41 H 5.24 N 9.39
Found: 62.38 5.36 9.42
R_f value: 0.55 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 99

4'-[[2-Methylmercapto-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-trifluoroacetate

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-methylmercapto-6-(pyrrolidinocarbonylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 96.1% of theory,
Melting point: 177-178°C
$C_{27}H_{26}N_4O_3S \times CF_3COOH$ (600.61)

Calculated:	C 57.99	H 4.53	N 9.33	
Found:	57.68	4.75	9.30	

R_f value: 0.52 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 100

4'-[[6-(2,3-Dimethylmaleic acid imido)-2-methylmercapto-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(2,3-dimethylmaleic acid imido)-2-methylmercapto-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 91.7% of theory,
Melting point: 276-277°C
$C_{28}H_{23}N_3O_4S$ (497.57)

Calculated:	C 67.59	H 4.66	N 8.45	S 6.44
Found:	67.57	4.94	8.40	6.37

R_f value: 0.47 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 101

4'-[[2-n-Butyl-6-[3-(7-nitrobenzofurazan-4-yl-amino)-propionylamino]benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl-hydrate

---

Prepared analogously to Example 55 from 4'-[[2-n-butyl-6-[3-(7-nitrobenzofurazan-4-yl-amino)-propionylamino]-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and 2 N hydrochloric acid in ethanol.
Yield: 33.3% of theory,
Melting point: 179-181°C
$C_{34}H_{31}N_{11}O_4 \times H_2O$ (675.70)

Calculated:	C 60.43	H 4.92	N 22.80
Found:	60.24	5.09	22.69

Example 102

4'-[[2-n-Butyl-6-[3-(7-nitrobenzofurazan-4-yl-amino)-propionylamino]benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-trifluoroacetate-hydrate

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-[3-(7-nitrobenzofurazan-4-yl-amino)-propionylamino]benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 87.5% of theory,
Melting point: 127°C (decomp.)
$C_{34}H_{31}N_7O_6 \times CF_3COOH \times H_2O$ (765.69)

Calculated:	C 56.47	H 4.47	N 12.80
Found:	56.68	4.27	12.67

Example 103

4'-[[6-(2,3-Dimethylmaleic acid imido)-2-methyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(2,3-dimethylmaleic acid imido)-2-methyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 94.4% of theory,
Melting point: 327-328°C
$C_{28}H_{23}N_3O_4$ (465.51)

	C	H	N
Calculated:	72.25	4.98	9.03
Found:	72.00	5.08	9.06

R_f value: 0.33 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 104

4'-[[6-(2,3-Dimethylmaleic acid imido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-semihydrate

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(2,3-dimethylmaleic acid imido)-benzimidazol-1-yl]-methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 95.5% of theory,
Melting point: 223-224°C
$C_{27}H_{21}N_3O_4 \times 0.5\ H_2O$ (460.49)

	C	H	N
Calculated:	70.42	4.82	9.13
Found:	70.30	4.88	8.81

R_f value: 0.34 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 105

4'-[[6-(2,3-Dimethylmaleic acid imido)-2-n-propyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid-monohydrate

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(2,3-dimethylmaleic acid imido)-2-n-propyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 92.5% of theory,
Melting point: 309-310°C
$C_{30}H_{27}N_3O_4 \times H_2O$ (511.58)

Calculated:	C 70.44	H 5.71	N 8.21
Found:	70.44	5.64	8.19

R_f value: 0.47 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 106

4'-[[6-(2,3-Dimethylmaleic acid imido)-2-ethyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[[6-(2,3-dimethylmaleic acid imido)-2-ethyl-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 87.5% of theory,
Melting point: 307-308°C
$C_{29}H_{25}N_3O_4$ (479.53)

Calculated:	C 72.64	H 5.25	N 8.76
Found:	72.41	5.37	8.94

R_f value: 0.40 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5 by volume)

Example 107

4'-[[2-Ethyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-ethyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 31% of theory,
Melting point: 183-185°C
$C_{31}H_{26}N_4O_2$ (486.60)

Calculated:	C 76.52	H 5.39	N 11.52
Found:	76.73	5.49	11.70

Example 108

4'-[[2-Methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 27% of theory,
Melting point: 173-175°C
$C_{26}H_{25}N_7O_2S$ (499.60)

Calculated:	C 62.51	H 5.04	N 19.63	S 6.42
Found:	62.39	5.05	19.44	6.33

Mass spectrum: m/e = 499

Example 109

4'-[[2-Methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 41 from 4'-[[2-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.

Yield: 26.5% of theory,
Melting point: 214-217°C
$C_{30}H_{24}N_8$ (496.80)

Calculated:	C 72.56	H 4.87	N 22.56
Found:	72.32	5.01	22.23

Example 110

4'-[[6-(Butanesultam-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 41 from 4'-[[6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 60.0% of theory,
Melting point: 246-249°C
$C_{25}H_{23}N_7O_2S$ (485.60)

Calculated:	C 61.84	H 4.77	N 20.19
Found:	61.75	4.92	20.28

Example 111

4'-[[2-Ethyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 41 from 4'-[[2-ethyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 41.0% of theory,
Melting point: from 178°C (sintering)
$C_{31}H_{26}N_8$ (510.60)

Calculated:	C 72.92	H 5.13	N 21.95
Found:	72.94	5.25	21.71

Mass spectrum: m/e = 510

Example 112

4'-[[2-Ethyl-6-(N-benzenesulphonyl-methylamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 41 from 4'-[[2-ethyl-6-(N-benzenesulphonyl-methylamino)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 66.0% of theory,
Melting point: 226-228°C
$C_{30}H_{27}N_7O_2S$ (549.70)

Calculated:	C 65.55	H 4.95	N 17.84	S 5.83
Found:	65.38	4.95	17.59	5.79

Example 113

4'-[[2-n-Propyl-6-(N-benzenesulphonyl-methylamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 41 from 4'-[[2-n-propyl-6-(N-benzenesulphonyl-methylamino)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 83.4% of theory,
Melting point: 177-179°C
$C_{31}H_{29}N_7O_2S$ (563.70)

Calculated:	C 66.05	H 5.18	N 17.40	S 5.69
Found:	65.89	5.14	17.21	5.73

Example 114

4'-[(2-n-Butyl-6-benzenesulphonyloxy-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.-butyl 4'-[(2-n-butyl-6-benzenesulphonyloxy-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.

Yield: 8.2% of theory,
Melting point: 193-195°C
$C_{31}H_{28}N_2O_5S$ (540.60)

Calculated:	C 68.92	H 5.22	N 5.18
Found:	68.94	5.08	5.08

Example 115

4'-[[2-n-Butyl-6-(3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 55 from 4'-[[2-n-butyl-6-(3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon-1-yl)-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and methanol in methanolic hydrochloric acid.
Yield: 28.0% of theory,
Melting point: from 125°C (decomp.)
$C_{36}H_{36}N_8O$ (596.80)

Calculated:	C 72.46	H 6.08	N 18.78
Found:	72.26	5.94	18.85

Example 116

4'-[[2-n-Butyl-5-(3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 55 from 4'-[[2-n-butyl-5-(3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon-1-yl)-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and methanol in methanolic hydrochloric acid.
Yield: 31.0% of theory,
Melting point: from 125°C (decomp.)
$C_{36}H_{36}N_8O$ (596.80)

Calculated:	C 72.46	H 6.08	N 18.78

Found: 72.27 6.03 18.61

Example 117

4'-[[2-n-Propyl-6-(3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 55 from 4'-[[2-n-propyl-6-(3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon-1-yl)-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and methanol in methanolic hydrochloric acid.
Yield: 35.0% of theory,
Melting point: from 132°C (decomp.)
$C_{35}H_{34}N_8O$ (582.71)
Calculated: C 72.14 H 5.88 N 19.23
Found: 71.98 6.02 19.11

Example 118

4'-[[2-Ethyl-6-(3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 55 from 4'-[[2-ethyl-6-(3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon-1-yl)-benzimidazol-1-yl]methyl]-2-(1-triphenylmethyl-tetrazol-5-yl)-biphenyl and methanol in methanolic hydrochloric acid.
Yield: 22.0% of theory,
Melting point: from 106°C (decomp.)
$C_{34}H_{32}N_8O$ (568.68)
Calculated: C 71.81 H 5.67 N 19.70
Found: 71.73 5.54 19.92

Example 119

4'-[[2-n-Butyl-6-(4,5-dihydro-2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

---

Prepared analogously to Example 64 from methyl 4'-[[2-n-butyl-6-(4,5-dihydro-2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl] biphenyl-2-carboxylate and sodium hydroxide solution in ethanol.
Yield: 80.0% of theory,
Melting point: 276-283°C
$C_{29}H_{28}N_4O_3$ (480.60)

Calculated:	C 72.48	H 5.87	N 11.66
Found:	72.20	6.13	11.53

Mass spectrum: m/e = 480

The following compounds are obtained analogously to Example 119:

4'-[[2-ethyl-6-(2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-butyl-6-(2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(2-methyl-4,5-dihydro-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

4'-[[2-n-propyl-6-(2-benzyl-4,5-dihydro-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Example 120

4'-[[2-n-Propyl-6-(4,5-dihydro-2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 64 from methyl 4'-[[2-n-propyl-6-(4,5-dihydro-2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl] biphenyl-2-carboxylate and sodium hydroxide solution in ethanol.
Yield: 66.0% of theory,
Melting point: 236-241°C
$C_{28}H_{26}N_4O_3$ (466.54)

Calculated:	C 72.09	H 5.62	N 12.01
Found:	71.88	5.61	11.95

Example 121

4'-[[2-Ethyl-6-(4,5-dihydro-2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 64 from methyl 4'-[[2-ethyl-6-(4,5-dihydro-2H-pyridazin-3-on-6-yl)-benzimidazol-1-yl]methyl] biphenyl-2-carboxylate and sodium hydroxide solution in ethanol.
Yield: 71.0% of theory,
Melting point: 255-257°C
$C_{27}H_{24}N_4O_3$ (452.51)

Calculated:	C 71.67	H 5.35	N 12.38
Found:	71.41	5.51	12.12

Example 122

4'-[[2-n-Butyl-6-(3-cyclohexyl-propylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.-butyl 4'-[[2-n-butyl-6-(3-cyclohexyl-propylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate and trifluoroacetic

acid in methylene chloride.

Yield: 85.7% of theory,

Melting point: 152-153°C

$C_{34}H_{11}N_3O_2 \times 0.75\ CF_3COOH$ (609.24)

Calculated:	C 69.99	H 6.91	N 6.90
Found:	70.02	6.93	6.84

R_f value: 0.24 (silica gel; ethyl acetate/ethanol/ammonia = 80:40:2 by volume)

In the Examples of Pharmaceutical Formulations which follow, any suitable compound of formula I, particularly compounds A to L of the pharmacological test report, may be used as the active substance:

Example I

Ampoules containing 50 mg of active substance per 5 ml

Active substance	50 mg
KH_2PO_4	2 mg
$Na_2HPO_4 \times 2H_2O$	50 mg
NaCl	12 mg
Water for injections ad	5 ml

Preparation:

The buffer substances and isotonic substance are dissolved in some of the water. The active substance is added and, once it has been completely dissolved, water is added to make up the required volume.

Example II

Ampoules containing 100 mg of active substance per 5 ml

Active substance	100 mg
Methyl glucamine	35 mg
Glycofurol	1000 mg
Polyethyleneglycol-polypropylene-glycol block polymer	250 mg
Water for injections ad	5 ml

Preparation:

Methyl glucamine is dissolved in some of the water and

the active substance is dissolved with stirring and heating. After the addition of solvents, water is added to make up the desired volume.

Example III

Tablets containing 50 mg of active substance

Active substance	50.0 mg
Calcium phosphate	70.0 mg
Lactose	40.0 mg
Corn starch	35.0 mg
Polyvinylpyrrolidone	3.5 mg
Magnesium stearate	1.5 mg
	200.0 mg

Preparation:

The active substance, $CaHPO_4$, lactose and corn starch are uniformly moistened with an aqueous PVP solution. The mass is passed through a 2 mm screen, dried at 50°C in a circulating air dryer and screened again.

After the lubricant has been added, the granules are compressed in a tablet making machine.

Example IV

Coated tablets containing 50 mg of active substance

Active substance	50.0 mg
Lysine	25.0 mg
Lactose	60.0 mg
Corn starch	34.0 mg
Gelatin	10.0 mg
Magnesium stearate	1.0 mg
	180.0 mg

Preparation:

The active substance is mixed with the excipients and moistened with an aqueous gelatin solution. After screening and drying, the granules are mixed with magnesium stearate and compressed to form tablet cores.

The cores thus produced are covered with a coating by known methods. A colouring may be added to the coating suspension or solution.

Example V

Coated tablets containing 100 mg of active substance

Active substance	100.0 mg
Lysine	50.0 mg
Lactose	86.0 mg
Corn starch	50.0 mg
Polyvinylpyrrolidone	2.8 mg
Microcrystalline cellulose	60.0 mg
Magnesium stearate	1.2 mg
	350.0 mg

Preparation:

The active substance is mixed with the excipients and moistened with an aqueous PVP solution. The moist mass is passed through a 1.5 mm screen and dried at 45°C. After drying, it is screened again and the magnesium stearate is added. This mixture is then compressed into cores.

The cores thus produced are covered with a coating by known methods. Colourings may be added to the coating suspension or solution.

Example VI

Capsules containing 250 mg of active substance

Active substance	250.0 mg
Corn starch	68.5 mg
Magnesium stearate	1.5 mg
	320.0 mg

Preparation:

The active substance and corn starch are mixed together and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The final mixture is packed into size 1 hard gelatine capsules.

Example VII

Oral suspension containing 50 mg of active substance per 5 ml

Active substance	50.0 mg
Hydroxyethylcellulose	50.0 mg
Sorbic acid	5.0 mg
70% sorbitol	600.0 mg
Glycerol	200.0 mg
Flavouring	15.0 mg
Water ad	5.0 ml

Preparation:

Distilled water is heated to 70°C. Hydroxyethyl-cellulose is dissolved therein with stirring. By the addition of sorbitol solution and glycerol the mixture is cooled to ambient temperature. At ambient

temperature, sorbic acid, flavouring and active substance are added. The suspension is evacuated with stirring to remove any air. One dose of 50 mg is contained in 5.0 ml.

Example VIII

Suppositories containing 100 mg of active substance

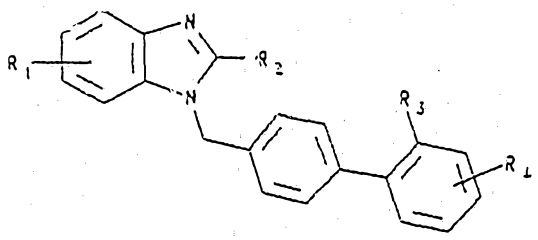
Active substance	100.0 mg
Solid fat	1600.0 mg
	1700.0 mg

Preparation:

The hard fat is melted. At 40°C the ground active substance is homogeneously dispersed in the melt. It is cooled to 38°C and poured into slightly chilled suppository moulds.

The claims defining the invention are as follows:

1. A compound of formula I



(I)

(wherein

R_1 represents a tetrahydrobenzimidazolyl or imidazopyridinyl group, a benzimidazolyl or benzoxazolyl group optionally substituted in the phenyl nucleus by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group, by a C_{1-3}-alkoxy or by a trifluoromethyl group, and in which the NH-group of the above-mentioned imidazole rings may additionally be substituted by a C_{1-6}-alkyl group or by a C_{3-7}-cycloalkyl group; an amino group substituted by a bicyclohexylcarbonyl or biphenylcarbonyl group; or a hydroxy(C_{5-7}-cycloalkyl)-aminocarbonyl group, which may additionally be substituted at the N-atom by a C_{1-3}-alkyl group; an aminocarbonylamino group substituted by a bicyclohexyl or biphenyl group and optionally also substituted by one or two C_{1-3}-alkyl groups at the N-atom; a 5-, 6- or 7-membered alkyleneimino or alkenyleneimino group optionally substituted by one or two C_{1-3}-alkyl groups or by a tetramethylene or pentamethylene group, in which a methylene group in the above mentioned alkylene and alkenylene moieties is replaced by a carbonyl or sulphonyl group; a 3,4,5,6-tetrahydro-2(1H)-pyrimidinone group optionally substituted by a C_{1-3}-alkyl or phenyl(C_{1-3}-alkyl) group; a straight-chained or branched hydroxy(C_{4-6}-alkyl)amino-carbonyl group; a maleic acid amido or maleic acid imido group optionally mono- or

disubstituted by a C_{1-3}-alkyl group or by a phenyl group, in which the substituents may be identical or different; an imidazoline or imidazole group optionally substituted by a C_{1-6}-alkyl group or by a C_{3-7}-cycloalkyl group; an imidazolidinedione group optionally substituted by a C_{1-3}-alkyl group, by a phenyl(C_{1-3}-alkyl) group or by a tetramethylene, pentamethylene or hexamethylene group; a C_{1-6}-alkylsulphonyloxy group; a benzenesulphonyloxy group optionally substituted by a C_{1-3}-alkyl group; a C_{1-3}-alkylamino or phenyl(C_{1-3}alkyl)amino group substituted by a C_{4-6}-alkylsulphonyl group or by a phenyl(C_{1-3}-alkyl)sulphonyl group; an amino or C_{1-3}alkylamino group substituted by a naphthalenesulphonyl group optionally substituted in the naphthalene ring by a di(C_{1-3}alkyl)-amino group or by one or two C_{1-3}-alkoxy groups; a C_{3-5}-alkoxy group substituted in the 3-, 4- or 5-position by an imidazolyl group; a C_{2-5}-alkoxy group substituted in the 2-, 3-, 4- or 5-position by a benzimidazolyl or tetrahydro-benzimidazolyl group; a pyridazin-3-one or dihydro-pyridazin-3-one group optionally substituted in the 2-position by an optionally phenyl-substituted C_{1-3}alkyl group and optionally additionally substituted at a carbon atom by 1 or 2 C_{1-3} alkyl groups; a pyrrolidino, piperidino or hexamethyleneimino group substituted by two C_{1-3}-alkyl groups; a 7-nitrobenzofurazan-4-yl-amino(C_{2-3}alkanoyl)amino group; a heptamethyleneimino, 1H,3H-quinazolin-2,4-dion-3-yl, pentamethylene-oxazolin-2-yl, benzofuran-carbonylamino or 7-nitro-benzofurazan-4-yl-amino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent an amino group substituted by a phenylsulphonyl, cyclohexylmethylaminocarbonyl, 2-carboxycyclohexyl-methylcarbonyl, 2-tert.butoxycarbonyl-cyclohexylmethyl-carbonyl, 2-carboxy-3,4,5,6-tetrahydrobenzoyl, N-methyl-phenylaminocarbonyl or 3-cyclohexylpropyl group; a

methylamino group substituted by a propylsulphonyl, phenylsulphonyl, methylphenylsulphonyl or chlorophenylsulphonyl group; an n-pentylamino group substituted by a phenylsulphonyl or methoxyphenylsulphonyl group; an n-propylamino group substituted by a methylphenylsulphonyl or methoxyphenylsulphonyl group; an isopropylamino group substituted by a benzoyl or chlorophenylsulphonyl group; an N-acetyl-cyclohexylmethylamino, 3,4,5,6-tetrahydrophthalimido, hexahydrohomophthalimido, N-methanesulphonyl-2-phenylethylamino, N-chlorophenylsulphonyl-benzylamino, piperidino, 4-methyl-piperidino or hexamethyleneimino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent a 2-oxo-1,2-dihydro-3,4-tetramethylene-pyrrolidin-1-yl, 3-carboxy-propionyl or 3-carboxy-2-methyl-propionyl group, and

where R_3 represents a carboxy group and R_2 represents a methyl, ethyl, n-propyl, n-butyl or methylmercapto group, R_1 in the 6-position may also represent a pyrrolidino-carbonylamino group, and

where R_3 represents a tetrazolyl group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent an n-pentylamino group substituted by a methyl-aminocarbonyl or cyclohexylaminocarbonyl group and R_1 in the 6-position may represent a 3,3-dimethyl-glutaric acid imido or 4,4-tetramethylene-glutaric acid imido group, and

where R_3 represents a tetrazolyl group and R_2 represents an ethyl or n-propyl group, R_1 in the 6-position may also represent an N-benzenesulphonyl-methylamino group, and

where R_3 represents a tert.butoxycarbonyl group and R_2

represents an n-butyl group, R_1 in the 6-position may also represent a 2-carboxycyclohexylmethylcarbonylamino or pyrrolidinocarbonylamino group;

R_2 represents a hydrogen atom or a straight-chained or branched C_{1-5}-alkyl group in which a methylene group may optionally be replaced by a sulphur atom;

R_3 represents a carboxy, cyano, 1H-tetrazolyl or 1-triphenylmethyl-tetrazolyl group or a (C_{1-4}alkoxy)-carbonyl group; and

R_4 represents a hydrogen, fluorine, chlorine or bromine atom);

and isomers and salts thereof.

2. A compound of formula I as claimed in claim 1 wherein

R_1 represents a tetrahydrobenzimidazolyl or imidazopyridinyl group, a benzimidazolyl group optionally substituted in the phenyl nucleus by a fluorine, chlorine or bromine atom, or by a methyl, methoxy or trifluoromethyl group, and in which the NH-group of the above-mentioned imidazole rings may additionally be substituted by a C_{1-6}-alkyl group or by a C_{3-6}-cycloalkyl group; a benzoxazol-2-yl group optionally substituted by a methyl group; an amino group substituted by a bicyclohexylcarbonyl, biphenylcarbonyl or benzofuryl-2-carbonyl group; an aminocarbonylamino group substituted in the 3-position by a bicyclohexyl or biphenyl group; a 5-, 6- or 7-membered alkyleneimino or alkenyleneimino group optionally substituted by one or two methyl groups or by a tetramethylene or pentamethylene group wherein a methylene group is replaced by a carbonyl or sulphonyl group; a 3,4,5,6-

tetrahydro-2(1H)-pyrimidinone group optionally substituted by a methyl or benzyl group; a hydroxy(C_4-alkyl)aminocarbonyl group, a maleic acid amido or maleic acid imido group optionally substituted by one or two substituents which may be the same or different selected from methyl and phenyl groups; an imidazolin-2-yl or imidazol-2-yl group substituted in the 1-position by a C_{1-6}-alkyl group or by a C_{3-7}-cycloalkyl group; an imidazolidinedione group optionally substituted by a methyl, benzyl, tetramethylene or pentamethylene group; a methylamino or benzylamino group substituted by a butanesulphonyl group or by a phenylmethanesulphonyl group; an amino or methylamino group substituted by a naphthalenesulphonyl group in which the naphthalene ring may be substituted by a dimethylamino group or by 2 methoxy groups, a pyridazin-3-one or dihydro-pyridazin-3-one group optionally substituted by a methyl or benzyl group; a pyrrolidino, piperidino or hexamethyleneimino group substituted by two methyl groups; a heptamethyleneimino, 1H,3H-quinazolin-2,4-dion-3-yl, hydroxycyclohexylamin -carbonyl, 4,5-pentamethylene-oxazolin-2-yl, 7-nitro-benzofurazan-4-yl-amino or 7-nitro-benzofurazan-4-yl-aminopropionylamino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent an amino group substituted by a phenylsulphonyl, cyclohexylmethylaminocarbonyl, 2-carboxycyclohexyl-methylcarbonyl, 2-tert.-butoxycarbonyl-cyclohexyl-methylcarbonyl, 2-carboxy-3,4,5,6-tetrahydrobenzoyl, N-methyl-phenylaminocarbonyl or 3-cyclohexylpropyl group; a methylamino group substituted by a propylsulphonyl, phenylsulphonyl, 4-methylphenylsulphonyl or 4-chlorophenylsulphonyl group; an n-pentylamino group substituted by a phenylsulphonyl or 4-methoxyphenyl-sulphonyl group; an n-propylamino group substituted by a 4-methylphenylsulphonyl or 4-methoxyphenylsulphonyl

group; an isopropylamino group substituted by a benzoyl or 4-chlorophenylsulphonyl group; an N-acetyl-cyclohexylmethylamino, 3,4,5,6-tetrahydrophthalimido, hexahydrohomophthalimido, N-methanesulphonyl-2-phenylethylamino, N-(4-chlorophenylsulphonyl)-benzylamino, piperidino, 4-methyl-piperidino or hexamethyleneimino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent a 2-oxo-1,2-dihydro-3,4-tetramethylene-pyrrolidin-1-yl, 3-carboxy-propionyl or 3-carboxy-2-methyl-propionyl group, and

where R_3 represents a carboxy group and R_2 represents a methyl, ethyl, n-propyl, n-butyl or methylmercapto group, R_1 in the 6-position may also represent a pyrrolidino-carbonylamino group, and

where R_3 represents a tetrazolyl group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent an n-pentylamino group substituted by a methylaminocarbonyl or cyclohexylaminocarbonyl group and R_1 in the 6-position may also represent a 3,3-dimethyl-glutaric acid imido or 4,4-tetramethylene-glutaric acid imido group, and

where R_3 represents a tetrazolyl group and R_2 represents an ethyl or n-propyl group, R_1 in the 6-position may also represent an N-benzenesulphonyl-methylamino group, and

where R_3 represents a tert.butoxycarbonyl group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent a 2-carboxy-cyclohexylmethylcarbonylamino or pyrrolidinocarbonylamino group;

R_2 represents a hydrogen atom or a straight-chained or

branched C_{1-4}-alkyl group in which a methylene group may be replaced by a sulphur atom;

R_3 represents a carboxy, cyano, 1H-tetrazolyl or 1-triphenylmethyl-tetrazolyl group or a (C_{1-4}alkoxy)-carbonyl group; and

R_4 represents a hydrogen, fluorine, chlorine or bromine atom;

and the 1-, 3-isomer mixtures and salts thereof with organic or inorganic acids or bases.

3. A compound of formula I as claimed in claim 1 or claim 2 wherein

R_1 in the 6-position represents a 1-methylbenzimidazol-2-yl, 3,4,5,6-tetrahydro-phthalimino, 2,3-diphenyl-maleic acid imido, 2,3-dimethyl-maleic acid imido, N-phenyl-methanesulphonyl-methylamino, 2-oxo-pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, 2-oxo-hexamethyleneimino, 2-oxo-3,4-tetramethylene-pyrrolidin-1-yl, 3,3-dimethylglutarimido, N-methylaminocarbonyl-n-pentylamino, propanesultam-1-yl or butanesultam-1-yl group;

R_2 represents a methyl, ethyl, n-propyl or n-butyl group;

R_3 represents a carboxy or 1H-tetrazolyl group; and

R_4 represents a hydrogen atom;

and the salts thereof with organic or inorganic acids or bases.

4. A compound as claimed in any one of claims 1 to 3 being

4'-[[2-n-propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid;

4'-[[2-n-butyl-6-(3,4,5,6-tetrahydro-phthalimino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid;

4'-[[2-n-butyl-6-(2,3-diphenyl-maleic acid imido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid;

4'-[[2-n-butyl-6-(2,3-dimethyl-maleic acid imido)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid;

4'-[[2-n-butyl-6-(N-phenylmethanesulphonyl-methylamino)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid;

4'-[[2-n-butyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

4'-[[2-n-butyl-6-(2-oxo-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

4'-[[2-n-butyl-6-(2-oxo-hexamethyleneimino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

4'-[[2-n-butyl-6-(3,3-dimethylglutarimido)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

4'-[[2-n-butyl-6-(N-methylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

4'-[[2-n-butyl-6-(cyclohexylaminocarbonyl-n-pentylamino)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

4'-[[2-n-butyl-6-(2-oxo-3,4-tetramethylene-pyrrolidin-1-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid;

4'-[[2-n-butyl-6-(propanesultam-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

4'-[[2-n-propyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

4'-[[2-n-butyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

4'-[[2-n-propyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl; or

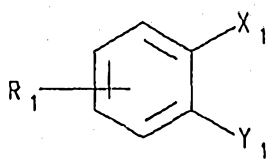
4'-[[2-n-propyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)-biphenyl;

or a salt thereof with an organic or inorganic acid or base.

5. A compound as claimed in any one of claims 1 to 4 being a physiologically acceptable salt of a compound of formula I.

6. A process for the prepartion of compounds as claimed in claim 1, said process comprising at least one of the following steps:

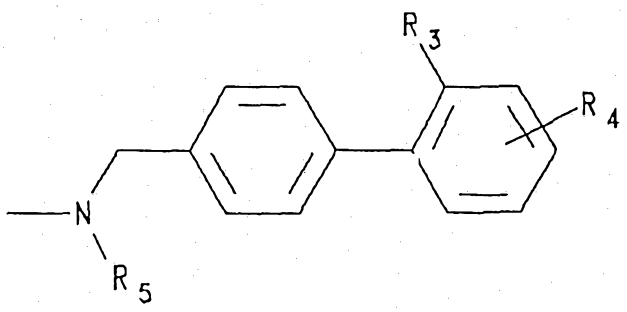
a) cyclising a compound of formula II



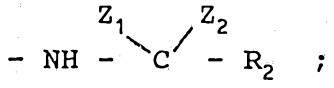
(II)

(wherein
R_1 is as defined in any one of claims 1 to 4;

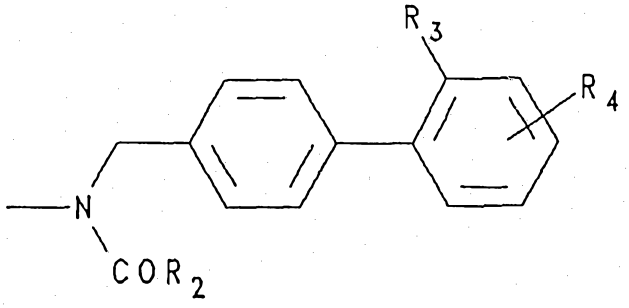
one of the groups X_1 or Y_1 represents a group of formula



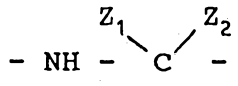
and the other group X_1 or Y_1 represents a group of formula



R_2, R_3 and R_4 are as defined in any one of claims 1 to 4,
R_5 represents a hydrogen atom or an R_2CO group;
Z_1 and Z_2, which may be the same or different, represent optionally substituted amino groups or hydroxy or mercapto groups optionally substituted by lower alkyl groups, or
Z_1 and Z_2 together represent an oxygen or sulphur atom, an imino group optionally substituted by a C_{1-3}-alkyl group, or a C_{2-3}-alkylenedioxy or C_{2-3}alkylenedithio group, with the proviso that one of the groups X_1 or Y_1 must represent a group of formula

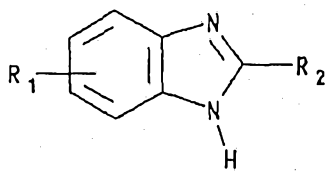


or



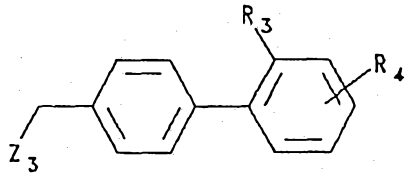
) or an N-oxide thereof and optionally subsequently reducing a cyclized N-oxide thus obtained;

b) reacting a benzimidazole of formula III



(III)

(wherein
R_1 and R_2 are as defined in any one of claims 1 to 4), with a biphenyl compound of formula IV

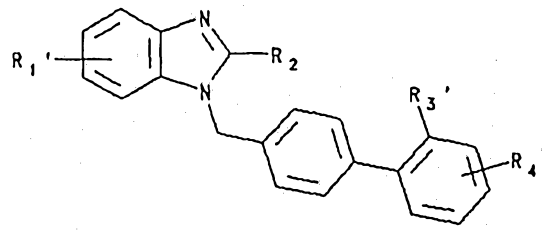


(IV)

(wherein
R_3 and R_4 are as defined in any one of claims 1 to 4; and
Z_3 represents a nucleophilic leaving group);

c) (to prepare a compound of formula I wherein R_3 represents a carboxy group)

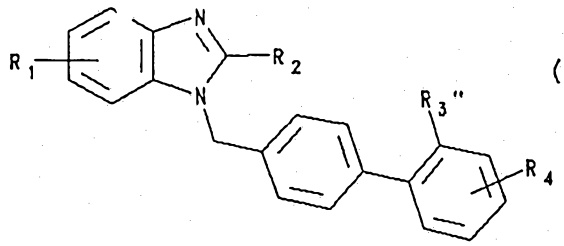
converting a compound of formula V



(V)

'wherein
R_2 and R_4 are as defined in any one of claims 1 to 4;
R_1' is a group R_1 as defined in any one of claims 1 to 4 or a 3-((C$_{1-3}$alkoxy)carbonyl)propionyl or 3-((C$_{1-3}$-alkoxy)carbonyl)-2-methylpropionyl group; and
R_3' represents a group which may be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis) into a corresponding carboxy compound; or

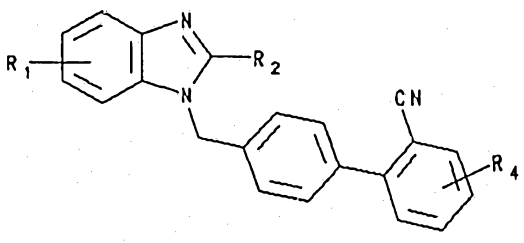
d) (to prepare a compound of formula I wherein R_3 represents a 1H-tetrazolyl group) cleaving a protecting group from a compound of formula VI



(VI)

(wherein
R_1, R_2 and R_4 are as defined in any one of claims 1 to 4; and
R_3" represents a 1H-tetrazolyl group protected in the 1- or 3-position by a protecting group);

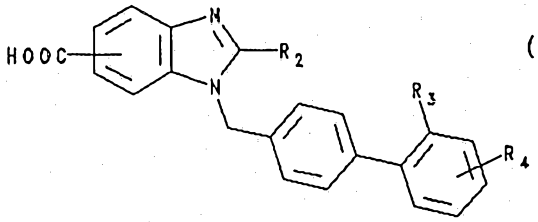
e) (to prepare a compound of formula I wherein R_3 represents a 1H-tetrazolyl group) reacting a compound of formula VII



(VII)

(wherein
R_1, R_2 and R_4 are as defined in any one of claims 1 to 4) with hydrazoic acid or a salt thereof;

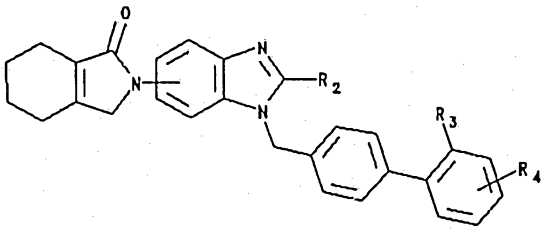
f) (to prepare compounds of formula I wherein R_1 represents a pentamethylene-oxazolin-2-yl group) reacting a compound of formula VIII



(VIII)

(wherein
R_2, R_3 and R_4 are as defined in any one of claims 1 to 4) with 1-aminomethyl-cyclohexanol in the presence of an acid-activating agent;

g) (to prepare a compound of formula I wherein R_1 represents a 2-oxo-3,4-tetramethylene-pyrrolidin-1-yl group) hydrogenating a compound of formula IX



(IX)

(wherein
R_2, R_3 and R_4 are as defined in any one of claims 1 to 4);

h) (to prepare compounds of formula I wherein R_1 represents an amino group substituted by a

bicyclohexylcarbonyl or biphenylcarbonyl group, which may additionally be substituted at the N-atom by a C_{1-3}-alkyl group, an aminocarbonylamino group substituted by a bicyclohexyl or biphenyl group and optionally additionally substituted by one or two C_{1-3}-alkyl groups at the N-atom, a maleic acid amido or maleic acid imido group optionally mono- or disubstituted by substituents selected from C_{1-3}-alkyl and phenyl groups, a C_{1-3}-alkylamino or phenyl(C_{1-3}alkyl)amino substituted by a C_{4-6}-alkylsulphonyl group or by a phenyl(C_{1-3}-alkyl)sulphonyl group, an amino or C_{1-3}alkylamino group substituted by a naphthalenesulphonyl group and optionally substituted in the naphthalene ring by a di(C_{1-3}alkyl)amino group or by one or two C_{1-3}-alkoxy groups, a 7-nitro-benzofurazan-4-yl-amino(C_{2-3}alkanoyl)amino group, a benzofurancarbonyl-amino or 7-nitro-benzofurazan-4-yl-amino group, and

where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent an amino group substituted by a phenylsulphonyl, cyclohexylmethylaminocarbonyl, 2-carboxycyclohexylmethylcarbonyl, 2-tert.-butoxycarbonyl-cyclohexylmethylcarbonyl, 2-carboxy-3,4,5,6-tetrahydrobenzoyl, N-methyl-phenylaminocarbonyl or 3-cyclohexylpropyl group, a methylamino group substituted by a propylsulphonyl, phenylsulphonyl, methylphenylsulphonyl or chlorophenylsulphonyl group, an n-pentylamino group substituted by a phenylsulphonyl or methoxyphenylsulphonyl group, an n-propylamino group substituted by a methylphenylsulphonyl or methoxyphenyl-sulphonyl group, an isopropylamino group substituted by a benzoyl or chlorophenylsulphonyl group, an N-acetyl-cyclohexylmethylamino, 3,4,5,6-tetrahydrophthalimido, hexahydrohomophthalimido, N-methanesulphonyl-2-phenylethylamino or N-chlorophenylsulphonyl-benzylamino group, and

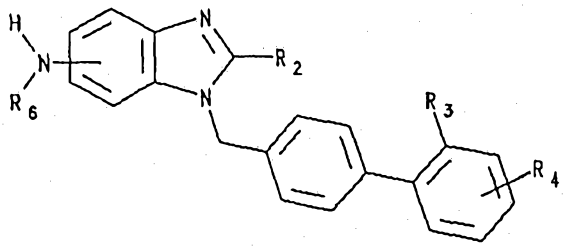
where R_3 represents a carboxy group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent a 2-oxo-1,2-dihydro-3,4-tetramethylene-pyrrolidin-1-yl group, and

where R_3 represents a carboxy group and R_2 represents a methyl, ethyl, n-propyl, n-butyl or methylmercapto group, R_1 in the 6-position may also represent a pyrrolidino-carbonylamino group, and

where R_3 represents a tetrazolyl group and R_2 represents an n-butyl group, R_1 in the 5- or 6-position may also represent an n-pentylamino group substituted by a methylamino-carbonyl or cyclohexylaminocarbonyl group and R_1 in the 6-position may also represent a 3,3-dimethyl-glutaric acid imido or 4,4-tetramethylene-glutaric acid imido group, and

where R_3 represents a tetrazolyl group and R_2 represents an ethyl or n-propyl group, R_1 in the 6-position may also represent an N-benzenesulphonyl-methylamino group, and

where R_3 represents a tert.-butoxycarbonyl group and R_2 represents an n-butyl group, R_1 in the 6-position may also represent a 2-carboxy-cyclohexylmethylcarbonylamino or pyrrolidinocarbonylamino group) reacting a compound of formula X



(X)

(wherein

R_2, R_3 and R_4 are as defined in any one of claims 1 to 4; and

R_6 represents a hydrogen atom, an n-pentyl, cyclohexylmethyl, C_{1-3}-alkyl or phenyl(C_{1-3}alkyl) group) with a compound of formula XI

$$Z_4 - W - R_7 \qquad (XI)$$

(wherein

Z_4 represents a nucleophilic leaving group;

W represents a -CO- or $-SO_2-$ group; and

R_7 represents a 2-hydroxycarbonyl-ethenyl group wherein the ethenyl moiety is mono- or disubstituted by substituents selected from C_{1-3}-alkyl and phenyl groups, a C_{3-6}-alkyl group, a phenyl(C_{1-3}alkyl) group, a naphthalene group optionally substituted by a di(C_{1-3}-alkyl)amino group or by one or two C_{1-3}alkoxy groups, a methyl, phenyl, methylphenyl, methoxyphenyl, chlorophenyl, biphenyl, bicyclohexyl, 2-carboxy-cyclohexylmethyl, 2-carboxy-3,4,5,6-tetrahydrophenyl, 3-carboxy-1,1-dimethyl-propyl, 3-carboxy-2,2-tetramethylene-propyl, 7-nitro-benzofurazan-4-yl-aminomethyl or 7-nitro-benzofurazan-4-yl-aminoethyl group, and

where W represents a -CO- group, R_7 may also represent an R_8NR_9 group wherein

R_8 represents a hydrogen atom or a C_{1-3}-alkyl group,

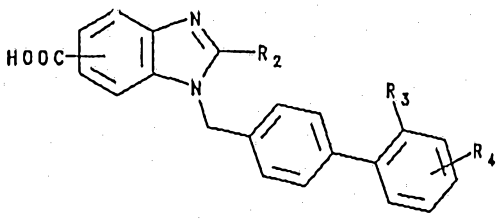
R_9 represents a methyl, cyclohexyl, cyclohexylmethyl, phenyl, biphenyl or bicyclohexyl group, or

R_8 and R_9 together with the nitrogen atom between them represent a pyrrolidino group, or

Z_4 together with R_9 represents another carbon-nitrogen bond, and

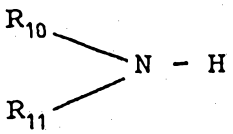
R_7 together with W may also represent a 7-nitro-benzofurazan-4-yl-amino group) or with a reactive derivative of a carboxylic acid of formula XI;

i) (to prepare compounds of formula I wherein R_1 represents a tetrahydrobenzimidazolyl or imidazopyridinyl group, a benzimidazolyl group optionally substituted in the phenyl nucleus by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group, by a C_{1-3}-alkoxy group or by a trifluoromethyl group, and in which the NH-group of the above-mentioned imidazole rings may additionally be substituted by a C_{1-6}-alkyl group or by a C_{3-7}-cycloalkyl group, a hydroxy(C_{3-7}-cycloalkyl)aminocarbonyl group, which may additionally be substituted at the N-atom by a C_{1-3}-alkyl group, or a straight-chained or branched hydroxy(C_{4-6}-alkyl)aminocarbonyl group) reacting a compound of formula XII



(XII)

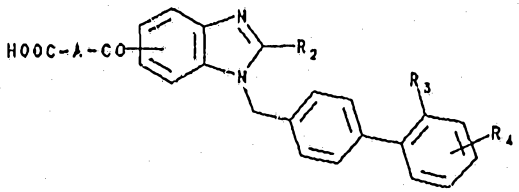
(wherein
R_2, R_3 and R_4 are as defined in any one of claims 1 to 4) or a reactive derivative thereof with an amine of formula XIII



(XIII)

(wherein
R_{10} represents a hydrogen atom, a cycloalkyl group or a C_{1-6}-alkyl group; and
R_{11} represents a C_{4-6}-hydroxyalkyl group, a C_{5-7}-hydroxycycloalkyl group or a 2-aminophenyl group which may be substituted in the phenyl nucleus by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group, by a C_{1-3}-alkoxy group or by a trifluoromethyl group, a 2-aminocyclohexyl or 2-aminopyridyl group) optionally with simultaneous decarboxylation;

j) (to prepare compounds of formula I wherein R_1 represents a dihydro-pyridazin-3-one or pyridazin-3-one group which may be substituted in the 2-position by an optionally phenyl-substituted C_{1-3}-alkyl group or at a carbon atom by one or two C_{1-3}-alkyl groups) reacting a carboxylic acid of formula XIV



(XIV)

(wherein
R_2, R_2, R_3 and R_4 are as defined in any one of claims 1 to 4; and
A represents an ethylene or ethenylene group optionally substituted by one or two C_{1-3}-alkyl groups) or a reactive acid derivative thereof with a hydrazine of formula XV

$$H_2N - NHR_{12} \qquad (XV)$$

(wherein
R_{12} represents a hydrogen atom or an optionally phenyl-substituted C_{1-3}-alkyl group);

k) resolving a 1-, 3-isomer mixture of a compound of formula I thus obtained by isomer separation into the 1- and 3-isomers thereof;

l) converting a compound of formula I thus obtained into a salt thereof or a salt of a compound of formula I into the free compound; and

m) carrying out a reaction according to any one of said steps (a) to (l) in which one or more groups are protected by a protecting group and subsequently removing any protecting group used.

7. A pharmaceutical composition comprising a compound of formula I as claimed in any one of claims 1 to 4 or a physiologically acceptable salt thereof together with at least one pharmaceutical carrier or excipient.

8. A method of treatment of the human or non-human animal body to combat hypertension, cardiac insufficiency, ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), cardiac insufficiency progression following myocardial infarction, diabetic nephropathy, glaucoma, gastrointestinal diseases and bladder diseases said method comprising administering to said body a compound of formula I as claimed in any one of claims 1 to 4 or a physiologically acceptable salt thereof.

9. A compound of formula I as claimed in claim 1 or a pharmaceutical composition thereof substantially as herein disclosed in any one of the Examples.

DATED this 9th day of June 1993.

DR KARL THOMAE GMBH

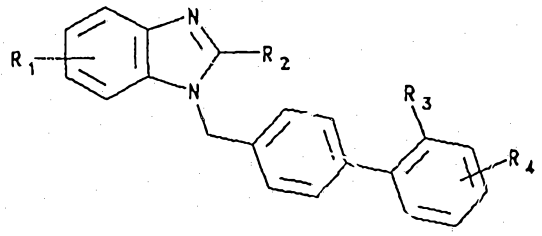
By their Patent Attorneys:

CALLINAN LAWRIE

Michael J. Hourihan.

Abstract

The invention relates to benzimidazoles of formula I



(I)

(wherein
R_1, R_2, R_3 and R_4 are as defined in claim 1) and the 1-, 3-isomer mixtures and the salts thereof, compounds which have valuable properties, in particular as angiotensin-II antagonists.