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(71) Applicant *(for all designated States except US)*: **Nycomed GmbH** [DE/DE]; Byk-Gulden-Str. 2, 78467 Konstanz (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BREHM, Christof** [DE/DE]; Rheinaustr. 16, 68163 Mannheim (DE). **ZIMMERMANN, Peter Jan** [DE/DE]; Wilhelmstr. 5, 71139 Ehningen (DE). **SENN-BILFINGER, Jörg** [DE/DE]; Säntisstrasse 7, 78464 Konstanz (DE). **PALMER, Andreas** [DE/DE]; Mägdebergstr. 2, 78224 Singen (DE). **BUHR, Wilm** [DE/DE]; Zum Kirchenwald 20, 78465 Konstanz (DE). **SIMON, Wolfgang-Alexander** [DE/DE]; Schubertstrasse 17, 78464 Konstanz (DE). **POSTIUS, Stefan** [DE/DE]; Austrasse 4b, 78467 Konstanz (DE). **KROMER, Wolfgang** [DE/DE]; Hinterhauserstr. 5, 78464 Konstanz (DE).

(74) Agents: **WILD, Robert** et al.; c/o Nycomed GmbH, P.O. Box 100310, 78403 Konstanz (DE).

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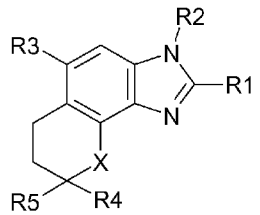
(54) Title: PHARMACEUTICALLY ACTIVE SPIRO-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES



(1)

(57) Abstract: The invention provides compounds of the formula (1), in which the substituents and symbols are as defined in the description. The compounds inhibit the secretion of gastric acid.

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Description

Title

PHARMACEUTICALLY ACTIVE SPIRO-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES

Technical field

The invention relates to novel compounds, which are used in the pharmaceutical industry as active compounds for the production of medicaments.

Background Art

In European patent application 266326 (which corresponds to US Patent 5,106,862), benzimidazole derivatives having a very broad variety of substituents are disclosed, which are said to be active as anti-ulcer agents. In the International Patent Application WO 97/47603 (Astra AB) benzimidazoles with a specific benzyloxy or benzylamino substitution are described.

The International Patent Application WO 04/054984 and WO 06/100254 disclose substituted, bicyclic benzimidazole derivatives which compounds are useful for treating gastrointestinal diseases.

The International Patent Applications WO 04/087701, WO 05/058893, WO 05/103057, WO 05/121139, WO 06/037748, WO 06/100255, WO 06/037759 and WO 06/136552 disclose tricyclic benzimidazole derivatives having different substitution patterns, which compounds are likewise useful for treating gastrointestinal diseases.

The International Patent Application WO 06/134111 discloses certain tricyclic benzimidazole derivatives being substituted by a spiro-dihydroindene group. These compounds are also useful for treating gastrointestinal diseases.

The International Patent Application WO 06/134112 discloses tricyclic imidazopyridine derivatives being substituted by a spiro-dihydroindene group. These compounds are also useful for treating gastrointestinal diseases

Disclosure of Invention

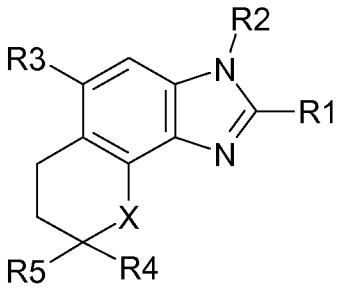
Technical problem

A whole series of compounds are known from the prior art, which inhibit gastric acid secretion by blockade of the H+/K+-ATPase. The compounds designated as proton pump inhibitors (PPI´s), for example omeprazole, esomeprazole, lansoprazole, pantoprazole or rabeprazole,

bind irreversibly to the H+/K+-ATPase. PPI´s are available as therapeutics for a long time already. A new class of compounds designated as reversible proton pump inhibitors (rPPI´s), as acid pump antagonists (APA´s) or as potassium competitive acid blockers (P-CAB´s) bind reversibly to the H+/K+-ATPase. Although rPPI´s, APA´s and P-CAB´s are known for more than 20 years and many companies are engaged in their development, at present rPPIs, APAs or P-CABs are available for therapy in a very limited manner only. The technical problem underlying the present invention is therefore to provide acid pump antagonists, which can be used in therapy.

Technical solution

The invention relates to compounds of the formula 1



(1)

in which

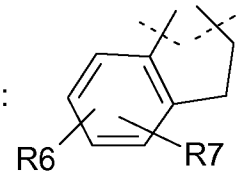
R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or hydroxy-1-4C-alkyl,

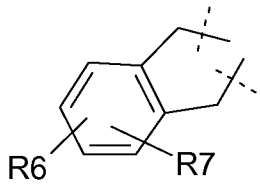
R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl or fluoro-1-4C-alkyl,

R3 is hydrogen, halogen, cyano, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,
or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R4 and R5 together form either a group G1 or a group G2

G1: 

G2: 

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, trifluoromethyl, halo-1-4C-alkoxy, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

X is O or NH

and their salts,

with the proviso that X does not have the meaning NH when R4 and R5 together form a group G2.

1-4C-Alkyl represents straight-chain or branched alkyl groups having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and the methyl group.

3-7C-Cycloalkyl represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkyl-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the aforementioned 3-7C-cycloalkyl groups. Examples which may be mentioned are the cyclopropylmethyl, the cyclohexylmethyl and the cyclohexylethyl group.

1-4C-Alkoxy represents groups, which in addition to the oxygen atom contain a straight-chain or branched alkyl group having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy group.

1-4C-Alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the aforementioned 1-4C-alkoxy groups. Examples which may be mentioned are the methoxymethyl group, the methoxyethyl group, in particular the 2-methoxyethyl group, the ethoxyethyl group, in particular the 2-ethoxyethyl group, the butoxyethyl group, in particular the 2-butoxyethyl group and the methoxypropyl, in particular the 3-methoxypropyl group.

1-4C-Alkoxycarbonyl (-CO-1-4C-alkoxy) represents a carbonyl group, to which one of the aforementioned 1-4C-alkoxy groups is bonded. Examples which may be mentioned are the methoxycarbonyl (CH_3O-C(O)-) and the ethoxycarbonyl group (CH_3CH_2O-C(O)-) .

2-4C-Alkenyl represents straight-chain or branched alkenyl groups having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butenyl, 3-butenyl, 1-propenyl and the 2-propenyl group (allyl group).

2-4C-Alkynyl represents straight-chain or branched alkynyl groups having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butynyl, 3-butynyl, and preferably the 2-propynyl, group (propargyl group).

Fluoro-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one or more fluorine atoms. Examples which may be mentioned are the trifluoromethyl group, the difluoromethyl, the 2-fluoroethyl, the 2,2-difluoroethyl or the 2,2,2-trifluoroethyl group.

Hydroxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by a hydroxy group. Examples which may be mentioned are the hydroxymethyl, the 2-hydroxyethyl, the 3-hydroxypropyl, the (2S)-2-hydroxypropyl and the (2R)-2-hydroxypropyl group. Hydroxy-1-4C-alkyl within the scope of the invention is understood to include 1-4C-alkyl groups substituted by two or more hydroxy groups. Examples which may be mentioned are the 3,4-dihydroxybutyl and in particular the 2,3-dihydroxypropyl groups.

Halogen within the meaning of the invention is bromo, chloro and fluoro.

1-4C-Alkoxy-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by a further 1-4C-alkoxy group. Examples which may be mentioned are the groups 2-(methoxy)ethoxy (CH_3-O-CH_2-CH_2-O-) and 2-(ethoxy)ethoxy (CH_3-CH_2-O-CH_2-CH_2-O-).

1-4C-Alkoxy-1-4C-alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkoxy-1-4C-alkyl groups, which is substituted by one of the aforementioned 1-4C-alkoxy groups. An example which may be mentioned is the group 2-(methoxy)ethoxymethyl (CH_3-O-CH_2-CH_2-O-CH_2-).

Fluoro-1-4C-alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by a fluoro-1-4C-alkoxy group. Fluoro-1-4C-alkoxy in this case represents one of the aforementioned 1-4C-alkoxy groups, which substituted by one or more fluorine atoms. Ex-

amples of fluoro-substituted 1-4C-alkoxy groups which may be mentioned are the 2-fluoroethoxy, 1,1,1,3,3,3-hexafluoro-2-propoxy, the 2-trifluoromethyl-2-propoxy, the 1,1,1-trifluoro-2-propoxy, the perfluoro-tert-butoxy, the 2,2,3,3,4,4,4-heptafluoro-1-butoxy, the 4,4,4-trifluoro-1-butoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy group. Examples of fluoro-1-4C-alkoxy-1-4C-alkyl radicals which may be mentioned are, 1,1,2,2-tetrafluoroethoxymethyl, the 2,2,2-trifluoroethoxymethyl, the trifluoromethoxymethyl, 2-fluoroethoxyethyl, the 1,1,2,2-tetrafluoroethoxyethyl, the 2,2,2-trifluoroethoxyethyl, the trifluoromethoxyethyl and preferably the difluoromethoxymethyl and the difluoromethoxyethyl radicals.

1-4C-Alkylcarbonyl represents a group, which in addition to the carbonyl group contains one of the aforementioned 1-4C-alkyl groups. An example which may be mentioned is the acetyl group.

1-4C-Alkylcarbonyl-1-4C-alkyl represents aforementioned 1-4C-alkyl groups which are substituted by 1-4C-alkylcarbonyl group. Examples which may be mentioned are the 2-oxo-propyl, the 2-oxo-butyl, the 2-oxo-pentyl, the 3-oxo-butyl or the 3-oxo-pentyl radicals.

Hydroxy-1-4C-alkoxy represents aforementioned 1-4C-alkoxy groups, which are substituted by a hydroxy group. A preferred example which may be mentioned is the 2-hydroxyethoxy group.

2-4C-Alkenyloxy represents groups, which in addition to the oxygen atom contain one of the abovementioned 2-4C-alkenyl groups. Examples, which may be mentioned, are the 2-butenyloxy, 3-butenyloxy and the 2-propenyloxy group (allyloxy group).

Carboxy-1-4C-alkyl represents 1-4C-alkyl groups which are substituted by a carboxyl group. Examples, which may be mentioned, are the carboxymethyl and the 2-carboxyethyl group.

1-4C-Alkoxycarbonyl-1-4C-alkyl represents 1-4C-alkyl groups, which are substituted by one of the abovementioned 1-4C-alkoxycarbonyl groups. Examples, which may be mentioned, are the Methoxycarbonylmethyl and the ethoxycarbonylmethyl group.

Halo-1-4C-alkoxy represents 1-4C-alkoxy groups which are completely or mainly substituted by halogen. "Mainly" in this connection means that more than half of the hydrogen atoms in the 1-4C-alkoxy groups are replaced by halogen atoms. Halo-1-4C-alkoxy groups are primarily chloro- and/or in particular fluoro-substituted 1-4C-alkoxy groups. Examples of halogen-substituted 1-4C-alkoxy groups which may be mentioned are the 2,2,2-trichloroethoxy, the hexachloroisopropoxy, the pentachloroisopropoxy, the 1,1,1-trichloro-3,3,3-trifluoro-2-propoxy, the

1,1,1-trichloro-2-methyl-2-propoxy, the 1,1,1-trichloro-2-propoxy, the 3-bromo-1,1,1-trifluoro-2-propoxy, the 3-bromo-1,1,1-trifluoro-2-butoxy, the 4-bromo-3,3,4,4-tetrafluoro-1-butoxy, the chlorodifluoromethoxy, the 1,1,1,3,3,3-hexafluoro-2-propoxy, the 2-trifluoromethyl-2-propoxy, the 1,1,1-trifluoro-2-propoxy, the perfluoro-tert-butoxy, the 2,2,3,3,4,4,4-heptafluoro-1-butoxy, the 4,4,4-trifluoro-1-butoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy group.

Mono- or di-1-4C-alkylamino represents an amino group, which is substituted by one or by two - identical or different - groups from the aforementioned 1-4C-alkyl groups. Examples which may be mentioned are the dimethylamino, the diethylamino and the diisopropylamino group.

1-4C-Alkylcarbonyl represents a group, which in addition to the carbonyl group contains one of the aforementioned 1-4C-alkyl groups. An example which may be mentioned is the acetyl group.

1-4C-Alkylcarbonylamino represents an amino group to which a 1-4C-alkylcarbonyl group is bonded. Examples which may be mentioned are the propionylamino ($C_3H_7C(O)NH$-) and the acetylamino group (acetamido group) ($CH_3C(O)NH$-) .

1-4C-Alkoxycarbonylamino represents an amino group, which is substituted by one of the aforementioned 1-4C-alkoxycarbonyl groups. Examples, which may be mentioned, are the ethoxycarbonylamino and the methoxycarbonylamino group.

1-4C-Alkoxy-1-4C-alkoxycarbonyl represents a carbonyl group, to which one of the aforementioned 1-4C-alkoxy-1-4C-alkoxy groups is bonded. Examples which may be mentioned are the 2-(methoxy)ethoxycarbonyl (CH_3-O-CH_2CH_2-O-CO-) and the 2-(ethoxy)ethoxycarbonyl group (CH_3CH_2-O-CH_2CH_2-O-CO-).

1-4C-Alkoxy-1-4C-alkoxycarbonylamino represents an amino group, which is substituted by one of the aforementioned 1-4C-alkoxy-1-4C-alkoxycarbonyl groups. Examples which may be mentioned are the 2-(methoxy)ethoxycarbonylamino and the 2-(ethoxy)ethoxycarbonylamino group.

Hydroxypyrrolidino represents a pyrrolidino group, which is substituted by a hydroxy group. Examples which may be mentioned are the 2-hydroxypyrrolidino and the 3-hydroxypyrrolidino groups.

Hydroxypiperidino represents a piperidino group, which is substituted by a hydroxy group. An example which may be mentioned is the 4-hydroxypiperidino group.

Hydroxyazetidino represents an azetidino group, which is substituted by a hydroxy group. An example which may be mentioned is the 3-hydroxyazetidino group.

N-1-4C-alkylpiperazino represents a piperazino group, in which one of the piperazino nitrogen atoms is substituted by one of the aforementioned 1-4-C-alkyl groups. Examples which may be mentioned are the 4-methylpiperazino, the 4-ethylpiperazino and the 4-iso-propylpiperazino groups.

1-4C-Alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl represents one of the aforementioned 1-4C-alkoxycarbonyl-1-4C-alkyl groups in which the 1-4C-alkyl is substituted by phenyl. An example which may be mentioned is the residue CH_3-O-C(O)-CH_2-CH(phenyl)-.

Carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl represents one of the aforementioned carboxy-1-4C-alkyl groups in which the 1-4C-alkyl is substituted by phenyl. An example which may be mentioned is the residue HO-C(O)-CH_2-CH(phenyl)-.

1-4C-Alkyl-thio-1-4C-alkyl represents one of the aforementioned 1-4C-alkoxy-1-4C-alkyl groups, in which the oxygen is replaced by sulfur. Examples which may be mentioned are the methyl-thio-methyl group, the methyl-thio-ethyl group, in particular the 2-methyl-thio-ethyl group, the ethyl-thio-ethyl group, in particular the 2-ethyl-thio-ethyl group, and the butyl-thio-ethyl group, in particular the 2-butyl-thio-ethyl group.

Possible salts of compounds of the formula 1 - depending on substitution - are especially all acid addition salts. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, malonic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid, trifluoracetic acid, ascorbic acid, lactic acid, D-glucuronic acid, lactobionic acid (4-O-beta-D-Galactopyranosyl-D-gluconic acid), galactaric acid, benzenesulfonic acid, laurylsulfonic acid or 3-hydroxy-2-naphthoic acid, where the acids are used in salt preparation - depending on whether a mono- or polybasic acid is concerned and on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

Salts of the compounds of formula I according to the invention can be obtained by dissolving, the free compound in a suitable solvent (for example a ketone such as acetone, methylethylketone or methylisobutylketone, an ether such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as methanol, ethanol or isopropanol) which contains the desired acid or to which the desired acid is then added, if necessary upon heating. The acid can be employed in salt preparation, depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired, in an equimolar quantitative ratio or one differing therefrom. The salts are obtained for example by evaporating the solvent or by precipitating upon cooling, by re-precipitating, or by precipitating with a non-solvent for the salt and separation, for example by filtration, of the salt after precipitation.

Pharmacologically intolerable salts, which can initially be obtained, for example, as process products in the production of the compounds according to the invention on the industrial scale, are converted into the pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention and their salts, if, for example, they are isolated in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula 1, and also all solvates and in particular all hydrates of the salts of the compounds of the formula 1.

Preferred are those compounds of the formula 1, in which

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

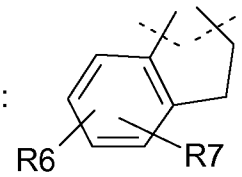
R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl, 1-4C-alkylthio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

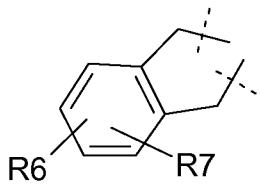
R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, aziridino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R4 and R5 together form either a group G1 or a group G2

G1: 

G2: 

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or halo-1-4C-alkoxy,

and their salts,

with the proviso that X does not have the meaning NH when R4 and R5 together form a group G2.

Emphasis is given to those compounds of the formula 1, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

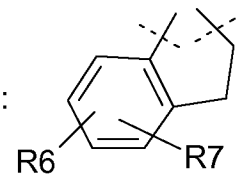
R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

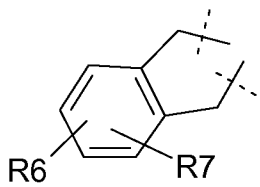
R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R4 and R5 together form either a group G1 or a group G2

G1: 

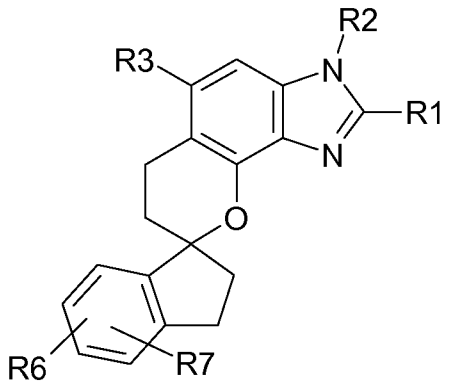
G2: 

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

and their salts

with the proviso that X does not have the meaning NH when R4 and R5 together form a group G2.

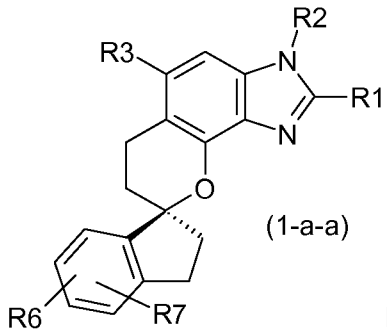
One aspect (aspect a) of the invention relates to compounds of the formula 1-a,



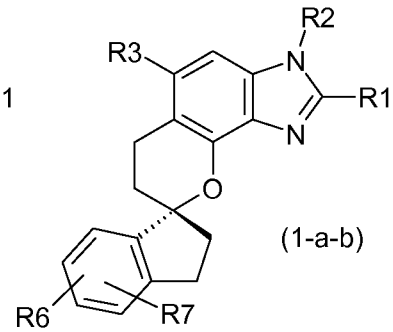
(1-a)

in which the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset.

Aspect a according to the invention therefore relates to compounds of the formula 1-a-a and 1-a-b, in which the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset.

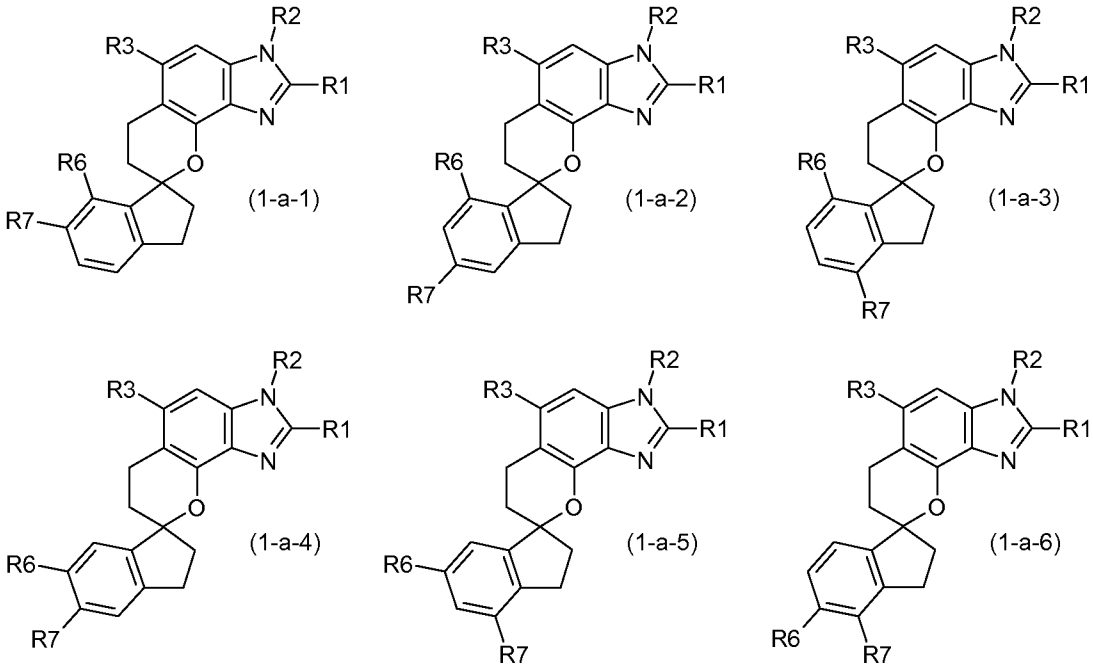


(1-a-a)



(1-a-b)

Different embodiments of aspect a relate to compounds of the formula 1-a-1 (aspect a, embodiment 1), 1-a-2 (aspect a, embodiment 2), 1-a-3 (aspect a, embodiment 3), 1-a-4 (aspect a, embodiment 4), 1-a-5 (aspect a, embodiment 5) and 1-a-6 (aspect a, embodiment 6).



in each of which embodiments 1-a-1, 1-a-2, 1-a-3, 1-a-4, 1-a-5 and 1-a-6, the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset.

A preferred embodiment of aspect a are the compounds of the formula 1-a-2, in which the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset.

Compounds of aspect a, which are to be mentioned are those, wherein

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or fluoro-1-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

R31 is hydrogen, hydroxyl, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hy-

droxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, 1-4C-alkoxy, halogen, trifluoromethyl or halo-1-4C-alkoxy,

and their salts.

Compounds of aspect a, which are to be particularly mentioned are those, wherein

R1 is hydrogen, 1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is hydrogen, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, 1-4C-alkoxy, halogen, trifluoromethyl or halo-1-4C-alkoxy,

and their salts.

Compounds of aspect a, which are to be emphasized are those, wherein

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, aziridino, morpholino, isoxazolidino,

tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or halo-1-4C-alkoxy,

and their salts.

Compounds of aspect a, which are to be particularly emphasized are those, wherein

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl or 3-7C-cycloalkyl,

R32 is hydrogen or 1-7C-alkyl,

or where

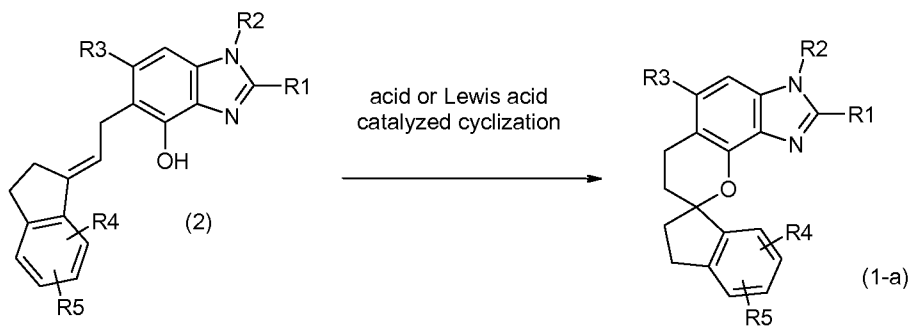
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, morpholino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

and their salts.

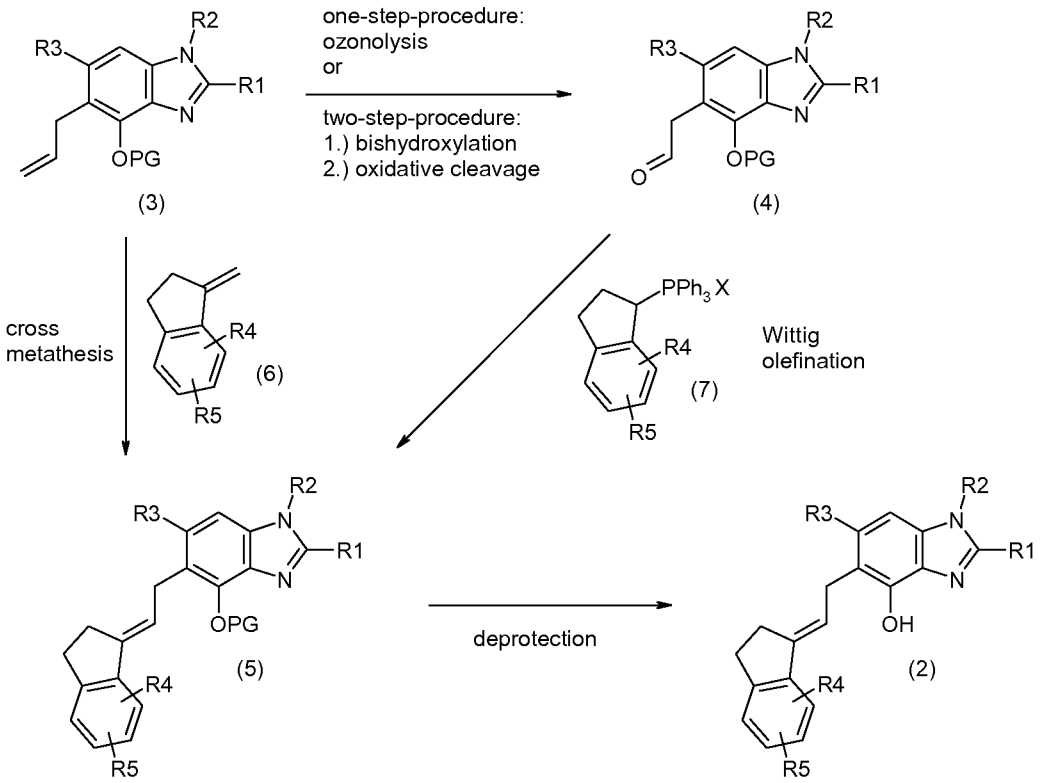
As outlined in scheme 1, the compounds of the formula 1-a can be obtained by cyclization of the unsaturated alcohols of the formula 2 under acidic or Lewis acidic conditions. Suitable reagents might be defined by the person skilled in the art or might be chosen from the following selection of acids and Lewis acids: formic acid, acetic acid, trifluoroacetic acid, phosphoric acid, sulfuric acid, fluorosulfonic acid, methanesulfonic acid, boron trifluoride, tin(IV) fluorosulfate (*Inorganic Chemistry* **1977**, 16, 1414-1417; *Chem. Commun.* **2005**, *17*, 2286-2288).

Scheme 1



Compounds of the formula 2 can be prepared for example as outlined in scheme 2.
The coupling of olefins of the formula 3 and 1-methyleneindanes of formula 6 can be performed by cross metathesis, preferably using suitable ruthenium pre-catalysts, e. g. the second generation Grubbs catalyst [246047-72-3], the Hoveyda-Grubbs catalyst (*Org. Biomol. Chem.* **2004**, *2*, 8), or the complexes described by Grubbs (*Angew. Chem.* **2002**, *114*, 4207), Blechert (*Angew. Chem.* **2002**, *114*, 2509; *Tetrahedron Lett.* **2003**, *44*, 2733) and Grela (*Angew. Chem.* **2002**, *114*, 4210; *J. Org. Chem.* **2004**, *69*, 6894; *The Chemical Record* **2006**, *6*, 144). Examples and reaction conditions for the performance of cross metathesis reactions can be found e.g. in *Angew. Chem.* **2003**, *115*, 1944; *The Chemical Record* **2006**, *6*, 144; *Aldrichimica Acta* **2003**, *36*, 93. The solvents dichloromethane, dichloroethane, toluene, and chlorobenzene represent a selection of solvents that are especially suitable for cross metathesis reactions. Typical reaction temperatures are in the range of room temperature to 80°C. The introduction of argon into the reaction vessel might be beneficial to remove ethylene formed in the course of the reaction and to increase the conversion.
Compounds of formula 5 (products of the cross metathesis reaction) can alternatively be obtained by a Wittig olefination reaction of aldehydes of formula 4 with phosphonium halogenides of formula 7 in the presence of a base (e.g. K_2CO_3, sodium methanolate, sodium hydride, or butyl lithium). Aldehydes of formula 4 can be synthesized from olefins of formula 3 using methodologies known to the expert, e.g. using ozonolysis procedures or via bishydroxylation (e.g. using alkaline $KMnO_4$, OsO_4, or catalytical amounts of OsO_4 together with a co-oxidant (e.g. N-methylmorpholine-N-oxide (NMO) or $K_3Fe(CN)_6$) followed by oxidative cleavage of the diol obtained (e.g. using periodic acid or lead tetracetate).

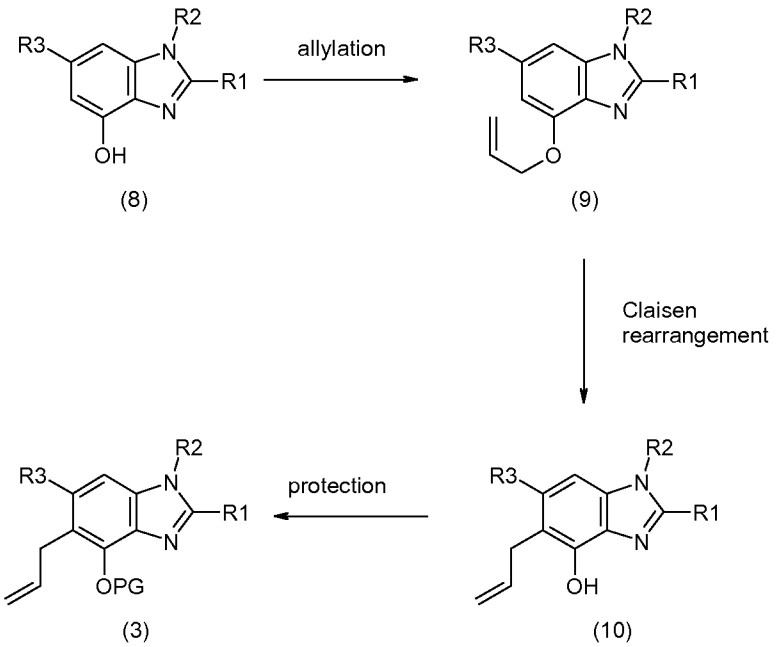
Scheme 2



The removal of the protective group present in compounds of the formula 5 to form compounds of formula 2 can be accomplished under standard conditions (e.g. using alkali hydroxides for the hydrolysis of acyl groups or tetrabutylammonium fluoride for the cleavage of silyl ethers). Suitable reaction conditions can be defined by the person skilled in art and can be based on the suggestions compiled in T. W. Greene / P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, J. Wiley & sons, New York, 1999.

Olefins of formula 3 can be synthesized following the reaction sequence as outlined in scheme 3. Allylation of 4-hydroxybenzimidazoles of formula 8, using methods known to the expert, and claisen rearrangement under thermal reaction conditions delivers 5-allyl-4-hydroxybenzimidazoles of formula 10. Treatment of compounds of the formula 10 with suitable electrophiles (e. g. alkyl halides, acyl halides, trialkylsilyl halides) furnishes O-protected derivatives of the formula 3. Suitable electrophiles (protecting groups) can be selected by the person skilled in art. The selection can be based e.g. on the protecting groups described in T. W. Greene / P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, J. Wiley & sons, New York, 1999.

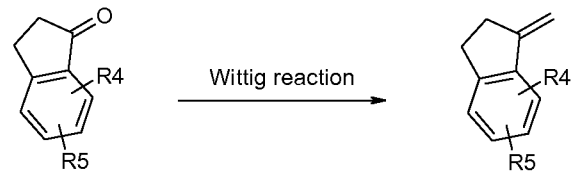
Scheme 3



(8) (9) (3) (10)

1-Methyleneindanes of the formula 6 can be synthesized from the corresponding 1-indanone derivatives of the formula 11 (scheme 4), using e.g. Wittig conditions (methyltriphenylphosphonium bromide and base, see e.g. *Aust. J. Chem.* **1972**, *25*, 1669; *J. Organomet. Chem.* **1995**, *502*, 169; *Molecules* **2005**, *10*, 217; *J. Org. Chem.* **1980**, *45*, 5247; *J. Am. Chem. Soc.* **1969**, *91*, 3558) or the diiodomethane, zinc, titanium tetrachloride system (*Tetrahedron Lett.* **1985**, *26*, 5579).

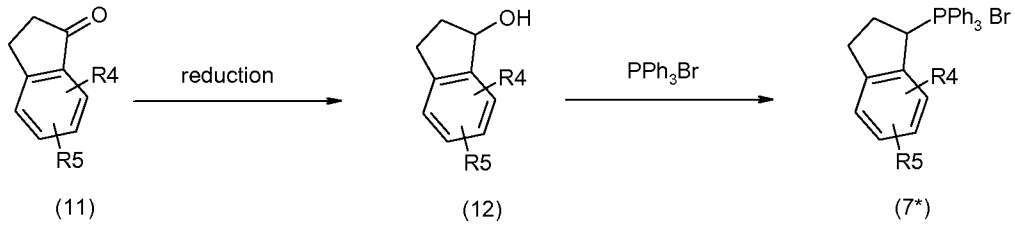
Scheme 4



(11) (6)

Phosphonium halogenides of formula 7 are known from the literature (e.g. Ulmschneider et al. *J. Med. Chem.* **2005**, *48*, *5*, 1572) or can be prepared as shown in scheme 5 for the synthesis of phosphonium bromides of formula 7* starting from 1-indanone derivatives of formula 11 in a two-step sequence.

Scheme 5

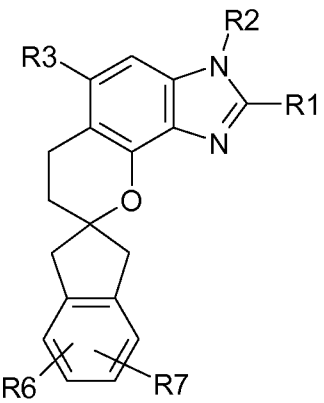


(11) (12) (7*)

1-Indanone derivatives of formula 11 are commercially available, can be prepared as described in the literature, for example 7-fluoro-1-indanone (P. Nguyen, *J. Org. Chem.* **2003**, *68*, *26*, 10195-10198), 7-hydroxy-1-indanone (Hayes et al. *J. Chem. Soc.* **1956**, 1585), or 7-methyl-1-indanone (E.D. Thorsett, F.R. Stermitz, *Synth. Commun.* **1972**, *2*, *6*, 375-381), or can be prepared by derivatization of 1-indanone derivatives in a manner known per se (for example by conversion of a group R4 or R5 into another group, e.g. conversion of a hydroxyl group into an alkoxy group).

4-Hydroxybenzimidazoles of formula 8 are known from the international patent application WO 2005/054984 or can be prepared by analogous methods.

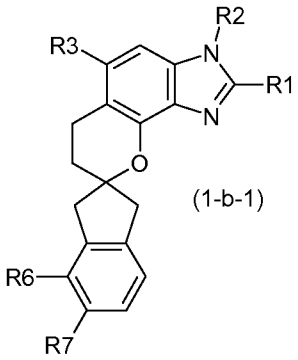
Another aspect (aspect b) of the invention relates to compounds of the formula 1-b,



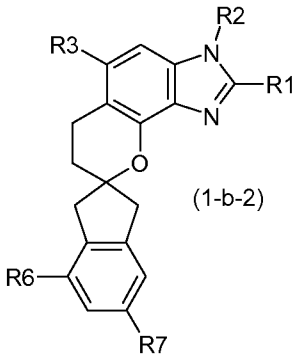
(1-b)

in which the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset.

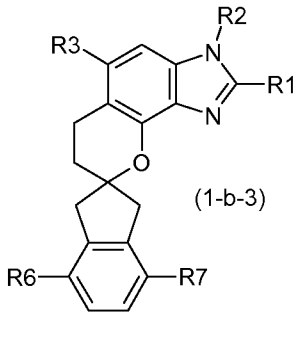
Different embodiments of aspect b relate to compounds of the formula 1-b-1 (aspect b, embodiment 1), 1-b-2 (aspect b, embodiment 2), 1-b-3 (aspect b, embodiment 3) and 1-b-4 (aspect b, embodiment 4).



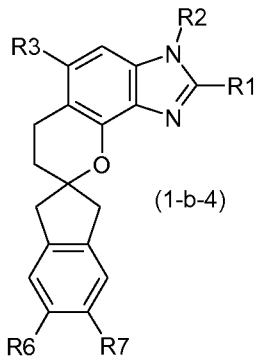
(1-b-1)



(1-b-2)



(1-b-3)



(1-b-4)

in each of which embodiments 1-b-1, 1-b-2, 1-b-3 and 1-b-4, the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset.

A preferred embodiment of aspect b are the compounds of the formula 1-b-3, in which the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset and in particular wherein R6 and R7 are identical.

Another preferred embodiment of aspect b are the compounds of the formula 1-b-4, in which the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset and in particular wherein R6 and R7 are identical.

Compounds of aspect b, which are to be mentioned are those, wherein

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or fluoro-1-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

R31 is hydrogen, hydroxyl, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, 1-4C-alkoxy, halogen, trifluoromethyl or halo-1-4C-alkoxy,

and their salts.

Compounds of aspect a, which are to be particularly mentioned are those, wherein

R1 is hydrogen, 1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, hydroxyl-1-4C-alkyl or halogen,

R3 is hydrogen, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, 1-4C-alkoxy, halogen, trifluoromethyl or halo-1-4C-alkoxy,

and their salts.

Compounds of aspect b, which are to be emphasized are those, wherein

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, aziridino, morpholino, isoxazolidino,

tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or halo-1-4C-alkoxy,

and their salts.

Compounds of aspect b, which are to be particularly emphasized are those, wherein

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen or 1-7C-alkyl,

or where

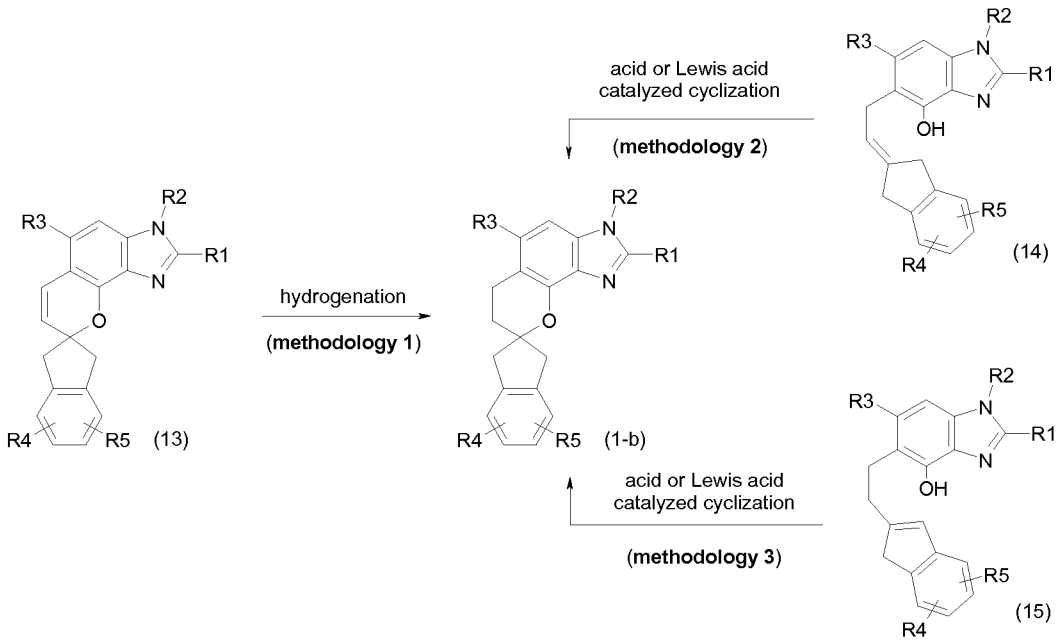
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, azetidino, isoxazolidino, tetrahydro-1,2-oxazino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are each hydrogen,

and their salts.

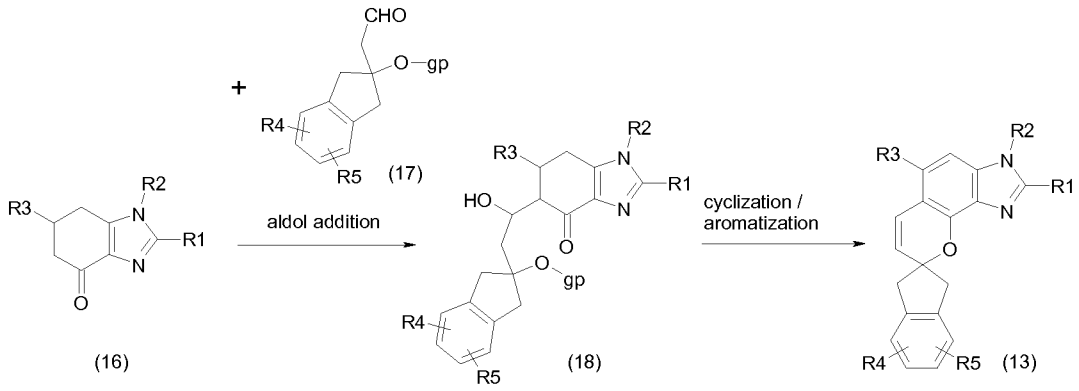
As outlined in scheme 6, the compounds of the formula 1-b can be obtained by application of different methodologies. Application of methodology 1 leads to compounds of the formula 1-b via hydrogenation of unsaturated compounds of the formula 13. Alternatively, compounds of formula 1-b can be synthesized by cyclization of the unsaturated alcohols of the formula 14 with an exocyclic double bond (methodology 2) or unsaturated alcohols of the formula 15 with an endocyclic double bond (methodology 3) under acidic or Lewis acidic conditions. Suitable reagents might be defined by the person skilled in the art or might be chosen from the following selection of acids and Lewis acids: formic acid, acetic acid, trifluoroacetic acid, phosphoric acid, sulfuric acid, fluorosulfonic acid, methanesulfonic acid, boron trifluoride, tin(IV) fluorosulfate (*Inorganic Chemistry* **1977**, 16, 1414-1417; *Chem. Commun.* **2005**, *17*, 2286-2288).

Scheme 6



Compounds of the formula 13 can be prepared for example as outlined in scheme 7. Aldol addition of ketones of the formula 16 to aldehydes of the formula 17 (the group gp comprises a protecting group, particularly a silyl protecting group e.g. the triethylsilyl protecting group) leads to aldol adducts of the formula 18 in which the group gp can either be the protecting group as outlined before or after cleavage during the aldol addition a hydrogen atom. If the cleavage of the group pg doesn't take place during the aldol addition, it has to be removed under standard conditions (e.g. using tetrabutylammonium fluoride for the cleavage of silyl ethers; suitable reaction conditions can be defined by the person skilled in art and can be based on the suggestions compiled in T. W. Greene / P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, J. Wiley & sons, New York, 1999). Cyclization (under acidic or Lewis acidic conditions) and aromatization (using standard aromatization reagents, e.g. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or chloranile) of aldol adducts of the formula 18 (with gp = hydrogen) leads to unsaturated compounds of the formula 13.

Scheme 7

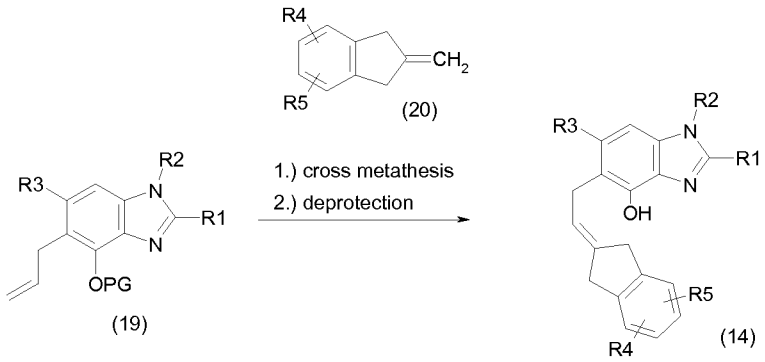


Unsaturated alcohols with an exocyclic double bond of the formula 14 can be prepared for example as outlined in scheme 8.

The coupling of olefins of the formula 19 and 2-methyleneindanes of formula 20 can be performed by cross metathesis, preferably using suitable ruthenium pre-catalysts, e. g. the second generation Grubbs catalyst [246047-72-3], the Hoveyda-Grubbs catalyst (*Org. Biomol. Chem.* **2004**, *2*, 8), or the complexes described by Grubbs (*Angew. Chem.* **2002**, *114*, 4207), Blechert (*Angew. Chem.* **2002**, *114*, 2509; *Tetrahedron Lett.* **2003**, *44*, 2733) and Grela (*Angew. Chem.* **2002**, *114*, 4210; *J. Org. Chem.* **2004**, *69*, 6894; *The Chemical Record* **2006**, *6*, 144). Examples and reaction conditions for the performance of cross metathesis reactions can be found e.g. in *Angew. Chem.* **2003**, *115*, 1944; *The Chemical Record* **2006**, *6*, 144; *Aldrichimica Acta* **2003**, *36*, 93. The solvents dichloromethane, dichloroethane, toluene, and chlorobenzene represent a selection of solvents that are especially suitable for cross metathesis reactions. Typical reaction temperatures are in the range of room temperature to 80°C. The introduction of argon into the reaction vessel might be beneficial to remove ethylene formed in the course of the reaction and to increase the conversion.

The removal of the protective group PG present in the cross coupling products can be accomplished under standard conditions (e.g. using alkali hydroxides for the hydrolysis of acyl groups or tetrabutylammonium fluoride for the cleavage of silyl ethers). Suitable reaction conditions can be defined by the person skilled in art and can be based on the suggestions compiled in T. W. Greene / P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, J. Wiley & sons, New York, 1999.

Scheme 8

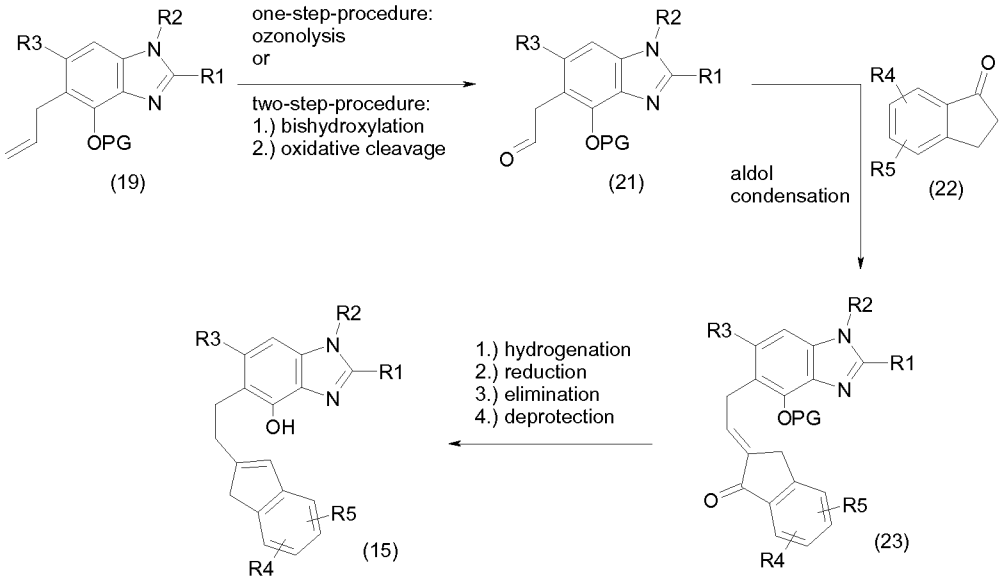


Unsaturated alcohols with an endocyclic double bond of the formula 15 can be prepared for example as outlined in scheme 9.

Aldehydes of the formula 21 can be synthesized from olefins of formula 19 using methodologies known to the expert, e.g. using ozonolysis procedures or via bishydroxylation (e.g. using alkaline $KMnO_4$, OsO_4, or catalytical amounts of OsO_4 together with a co-oxidant (e.g. N-methylmorpholine-N-oxide (NMO) or $K_3Fe(CN)_6$) followed by oxidative cleavage of the diol obtained (e.g. using periodic acid or lead tetracetate).

Aldol addition (under basic conditions e.g. using bases as lithium bis(trimethylsilyl)amide , lithium diisopropylamide or sodium methanolate) and aldol condensation (under acidic conditions e.g. using acids as sulphuric acid) of these aldehydes of the formula 21 with 1-indanones of the formula 22 delivers aldol products of the formula 23. Finally, compounds of the formula 15 with an exocyclic double bond can be prepared via a four step procedure: i.) hydrogenation e.g. using platinum oxid or palladium on charcoal; ii.) reduction e.g. using sodium boronhydride; iii.) elimination e.g. under acidic conditions e.g. using acids as hydrochloric acid or sulphuric acid; iv.) removal of the protecting group PG under standard conditions e.g. using alkali hydroxides for the hydrolysis of acyl groups or tetrabutylammonium fluoride for the cleavage of silyl ethers.

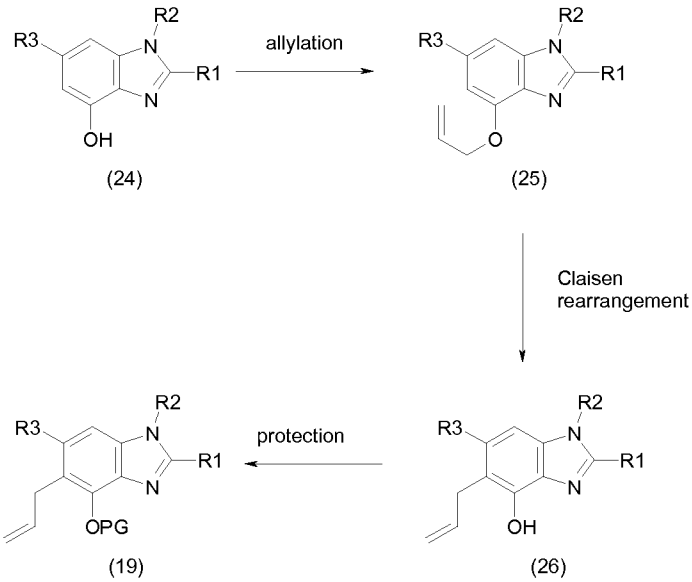
Scheme 9



Olefins of formula 19 can be synthesized following the reaction sequence as outlined in scheme 10.

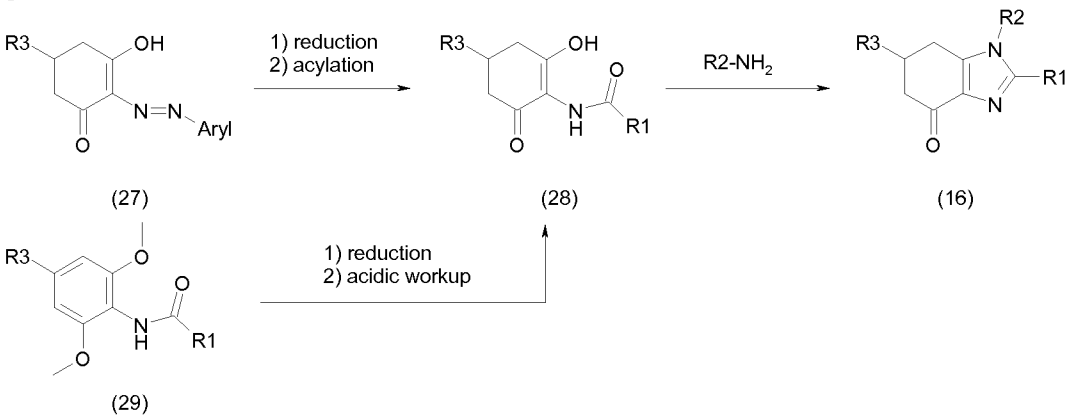
Allylation of 4-hydroxybenzimidazoles of formula 24, using methods known to the expert, and claisen rearrangement under thermal reaction conditions delivers 5-allyl-4-hydroxybenzimidazoles of formula 26. Treatment of compounds of the formula 26 with suitable electrophiles (e. g. alkyl halides, acyl halides, trialkylsilyl halides) furnishes O-protected derivatives of the formula 19. Suitable electrophiles (protecting groups) can be selected by the person skilled in art. The selection can be based e.g. on the protecting groups described in T. W. Greene / P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, J. Wiley & sons, New York, 1999.

Scheme 10



Ketones of the formula 16 can be prepared as shown, for example, in scheme 11 performing the cyclization reaction of compounds of the formula 28 in the presence of a primary amine (R2 ≠ H) or ammonia (R2 = H) under conditions known to the expert. The preparation of compounds of the formula 28 can be achieved by several methodologies known to the expert; two examples are illustrated in scheme 11. The reduction and subsequent acylation of azo-compounds of the formula 27 is performed in a manner known to the expert, for example as described by A. Treibs, R. Zinsmeister in *Chem. Ber.* **1957**, *90*, 87-92. Alternatively, aromatic compounds of the formula 29 can be reduced by strong reducing agents followed by an acidic workup, for example as described by Kuehne, Lambert in *Org. Synth.*; Coll. Vol. V, **1973**, 400 or by A. Mann, C. Humblet in *J. Med. Chem.*, **1985**, *28*, 1440-1446. Compounds of the formula 27 or 29 are known, for example from the patent FR2242984, or from Allan, *Collect. Czech. Chem. Commun.* **1966**, *31*, 4129, or they can be prepared using analogues process steps.

Scheme 11

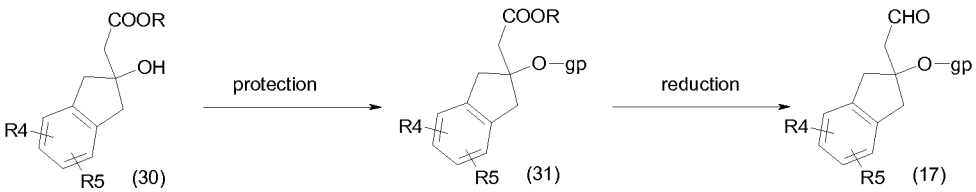


Aldehydes of the formula 17 can be prepared as outlined in the following scheme 12.

The hydroxyl group of hydroxyesters of the formula 30 can be protected by a group gp (e.g. silyl groups, particularly the triethylsilyl group or the tert.-butyldimethylsilyl group) by several methodologies known to the expert (e.g. using silyl triflate in the presence of imidazole) forming compounds of the formula 31. Selective reduction of the ester group in compounds of the formula 31 forming aldehydes of the formula 17 can be performed by methods known to the expert (e.g. using diisobutylaluminium hydride).

Hydroxyesters of the formula 30 can be prepared as described in the literature, for example the synthesis of ethyl (2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)acetate is described by H. Ahmed, N. Campbell, *J. Chem. Soc.* **1960**, 4115-4120.

Scheme 12

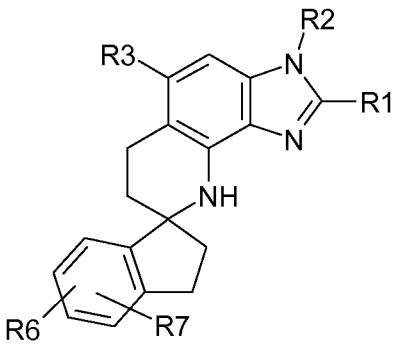


1-Indanone derivatives of formula 22 are commercially available, can be prepared as described in the literature, for example 7-fluoro-1-indanone (P. Nguyen, *J. Org. Chem.* **2003**, *68*, *26*, 10195-10198), 7-hydroxy-1-indanone (Hayes et al. *J. Chem. Soc.* **1956**, 1585), or 7-methyl-1-indanone (E.D. Thorsett, F.R. Stermitz, *Synth. Commun.* **1972**, *2*, *6*, 375-381), or can be prepared by derivatization of 1-indanone derivatives in a manner known per se (for example by conversion of a group R4 or R5 into another group, e.g. conversion of a hydroxyl group into an alkoxy group).

4-Hydroxybenzimidazoles of formula 24 are known from the international patent application WO 2005/054984 or can be prepared by analogous methods.

2-Methyleneindanes of the formula 20 can be synthesized from the corresponding 2-indanone derivatives using one of the methods described in *Organic Lett.* **2004**, 6, 4961 {magnesium, titanium tetrachloride}, *J. Org. Chem.* **1987**, *52*, 281 {cer(III) chloride, [(trimethylsilyl)methyl]lithium, followed by treatment with an acid}, or *J. Am. Chem. Soc.* **1978**, *100*, 7352 {methyltriphenylphosphonium bromide, base}. Alternatively, 2-methyleneindanes can be synthesized via a Palladium-catalyzed cyclization reaction as described in *J. Org. Chem.* **1989**, *54*, 2507.

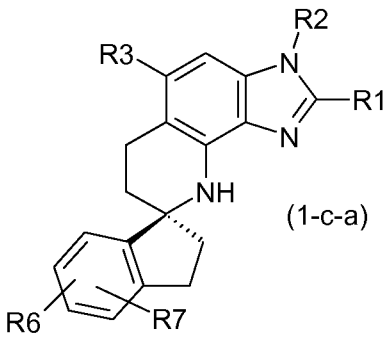
Still another aspect (aspect c) of the invention relates to compounds of the formula 1-c,



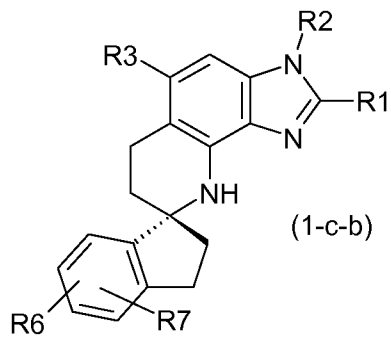
(1-c)

in which the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset.

Aspect c according to the invention therefore relates to compounds of the formula 1-c-a and 1-c-b, in which the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset.

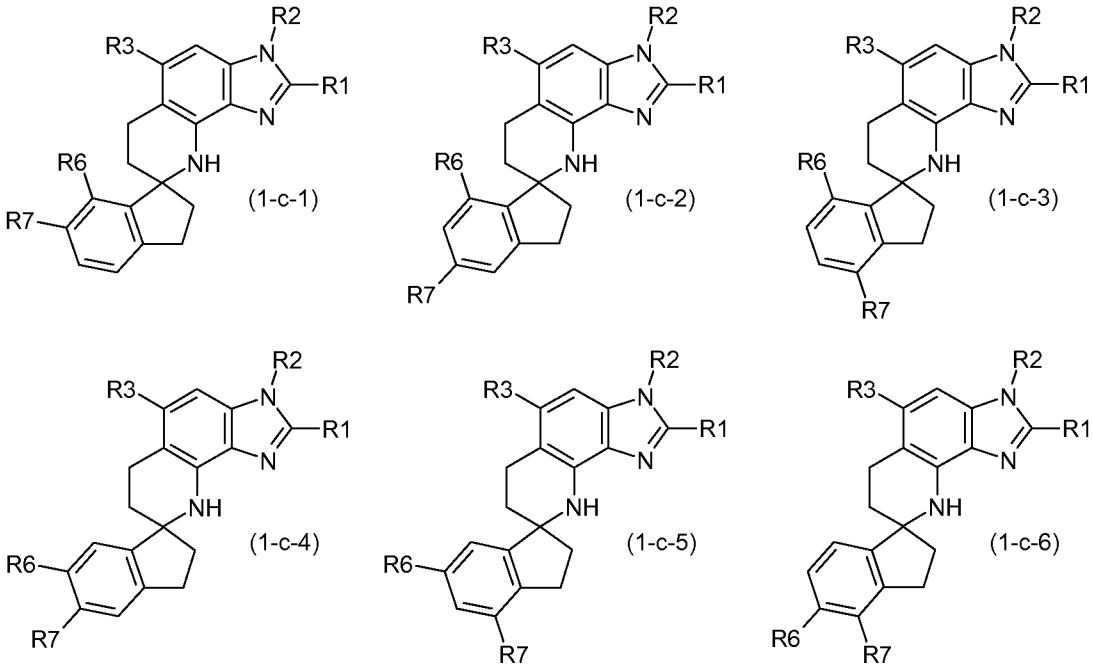


(1-c-a)



(1-c-b)

Different embodiments of aspect c relate to compounds of the formula 1-c-1 (aspect c, embodiment 1), 1-c-2 (aspect c, embodiment 2), 1-c-3 (aspect c, embodiment 3), 1-c-4 (aspect c, embodiment 4), 1-c-5 (aspect c, embodiment 5) and 1-c-6 (aspect c, embodiment 6).



in each of which embodiments 1-c-1, 1-c-2, 1-c-3, 1-c-4, 1-c-5 and 1-c-6, the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset.

A preferred embodiment of aspect c are the compounds of the formula 1-c-2, in which the substituents R1, R2, R3, R6 and R7 have the meanings as indicated in the outset.

Compounds of aspect c, which are to be mentioned are those, wherein

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or fluoro-1-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

R31 is hydrogen, hydroxyl, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, 1-4C-alkoxy, halogen, trifluoromethyl or halo-1-4C-alkoxy,

and their salts.

Compounds of aspect c, which are to be particularly mentioned are those, wherein

R1 is hydrogen, 1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, hydroxyl-1-4C-alkyl or halogen,

R3 is hydrogen, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, 1-4C-alkoxy, halogen, trifluoromethyl or halo-1-4C-alkoxy,

and their salts.

Compounds of aspect c, which are to be emphasized are those, wherein

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, aziridino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or halo-1-4C-alkoxy,

and their salts.

Compounds of aspect c, which are to be particularly emphasized are those, wherein

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is 1-7C-alkyl,

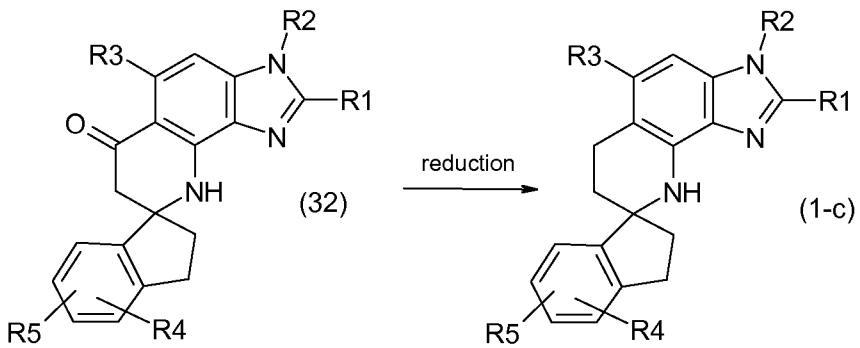
R32 is hydrogen or 1-7C-alkyl,

R6 and R7 are each hydrogen,

and their salts.

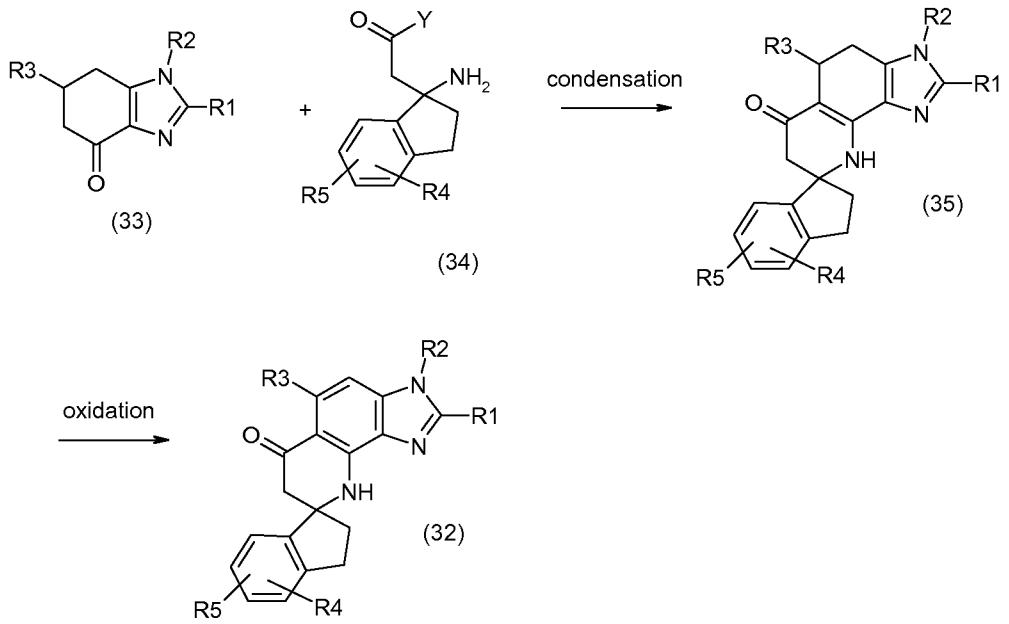
As outlined in scheme 13, the compounds of the formula 1-c can be obtained by reduction of the carbonyl group in the corresponding compounds of the formula 32 by methods which are familiar to a person skilled in the art, for example using triethylsilane / trifluoroacetic acid (West et al., J. Org. Chem. 1973, 38, 2675-2681) or, for example using lithium aluminium hydride in the case when R3 is a group which can not be reduced under these conditions like for example R3 = hydrogen or by catalytic hydrogenation.

Scheme 13



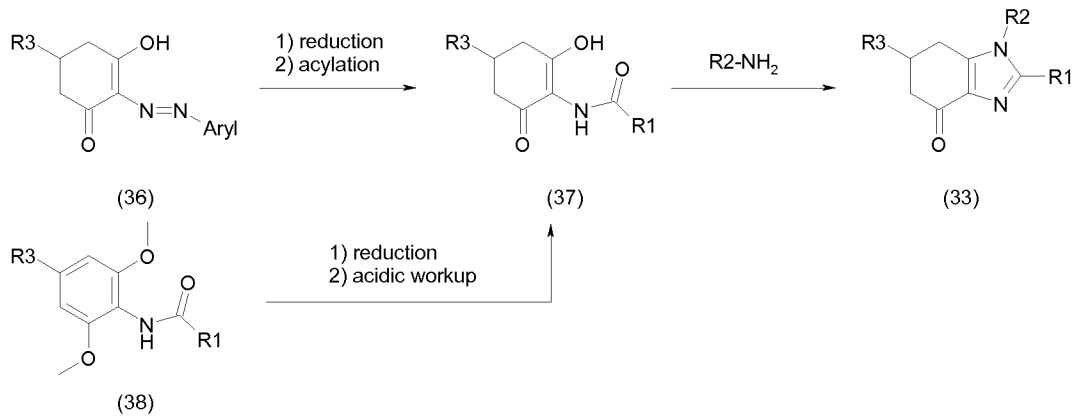
Compounds of the formula 32 can be prepared for example as outlined in scheme 14. In a first step ketones of the formula 33 are reacted with spiro-amino acid derivatives of the formula 34 (wherein Y is a suitable leaving group, for example an 1-4C-alkoxy group, e.g. an ethoxy group) to give compounds of the formula 35. In a second step, compounds of the formula 35 are oxidized by standard procedures using a suitable oxidizing agent (e.g. chloranil or 2,3-dichloro-5,6-dicyanobenzoquinone) to give compounds of the formula 32.

Scheme 14



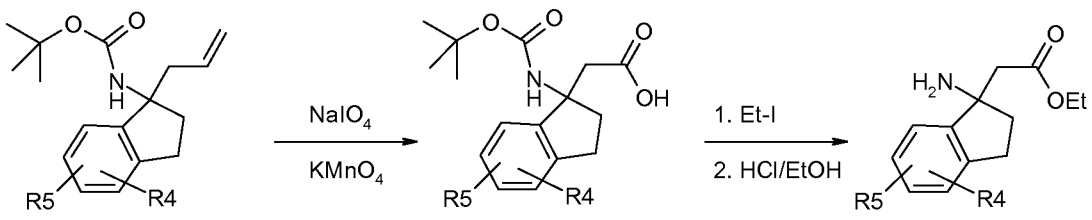
Ketones of the formula 33 can be prepared as shown, for example, in scheme 15 performing the cyclization reaction of compounds of the formula 37 in the presence of a primary amine (R2 ≠ H) or ammonia (R2 = H) under conditions known to the expert. The preparation of compounds of the formula 37 can be achieved by several methodologies known to the expert; two examples are illustrated in scheme 15. The reduction and subsequent acylation of azo-compounds of the formula 36 is performed in a manner known to the expert, for example as described by A. Treibs, R. Zinsmeister in Chem. Ber. 1957, 90, 87-92. Alternatively, aromatic compounds of the formula 38 can be reduced by strong reducing agents followed by an acidic workup, for example as described by Kuehne, Lambert in Org. Synth.; Coll. Vol. V, 1973, 400 or by A. Mann, C. Humblet in J. Med. Chem., 1985, 28, 1440-1446. Compounds of the formula 36 or 38 are known, for example from the patent FR2242984, or from Allan, Collect. Czech. Chem. Commun. 1966, 31, 4129, or they can be prepared using analogous process steps.

Scheme 15



As outlined in scheme 16, the required ß-amino acid derivatives of the general formula 34 can be prepared from the corresponding tert-butoxycarbonyl-protected allyl amines of the formula 39* by methods familiar to the expert and as described in literature, e.g. by oxidative cleavage with potassium permanganate and sodium (meta)periodate (L. Munoz et al., J. Org. Chem. 2001, 66, 4206-4213) and subsequent esterification and deprotection of the intermediate protected ß-amino acid of the formula 34*. The esterification of tert-butoxycarbonyl-protected ß-amino acids 34* is carried out in a manner known per se, for example by reaction of 34* with alkyl halogenides, e.g. ethyl iodide, under basic reaction conditions. Subsequent removal of the tert-butoxycarbonyl group to give ß-amino esters 34 is achieved by treatment with acids, preferentially with ethanolic hydrogen chloride.

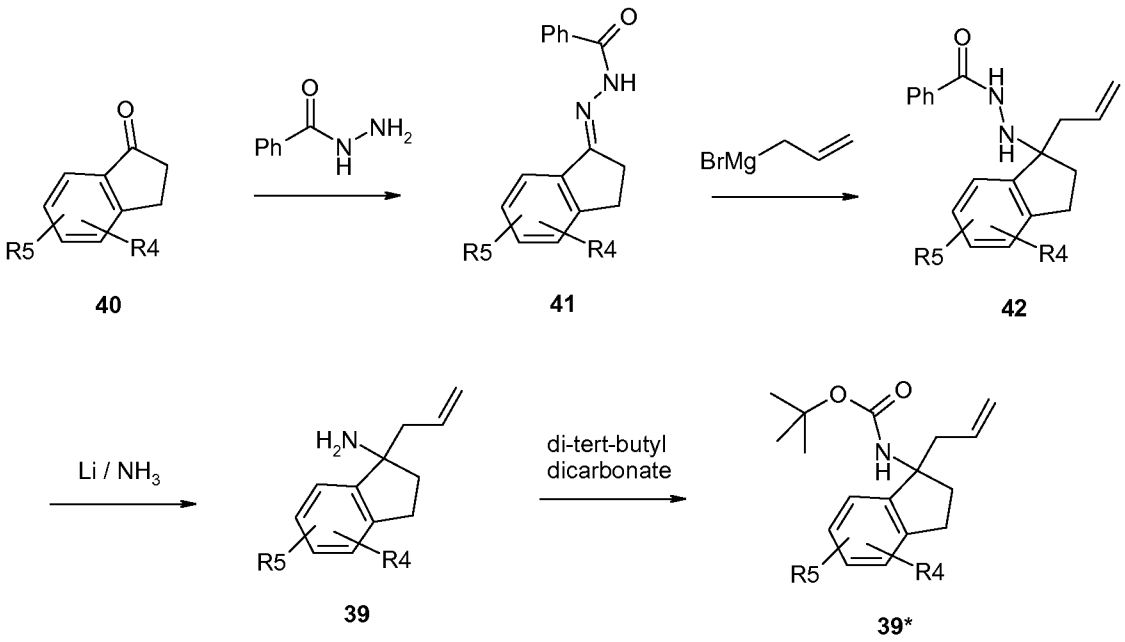
Scheme 16



39* **34*** **34**

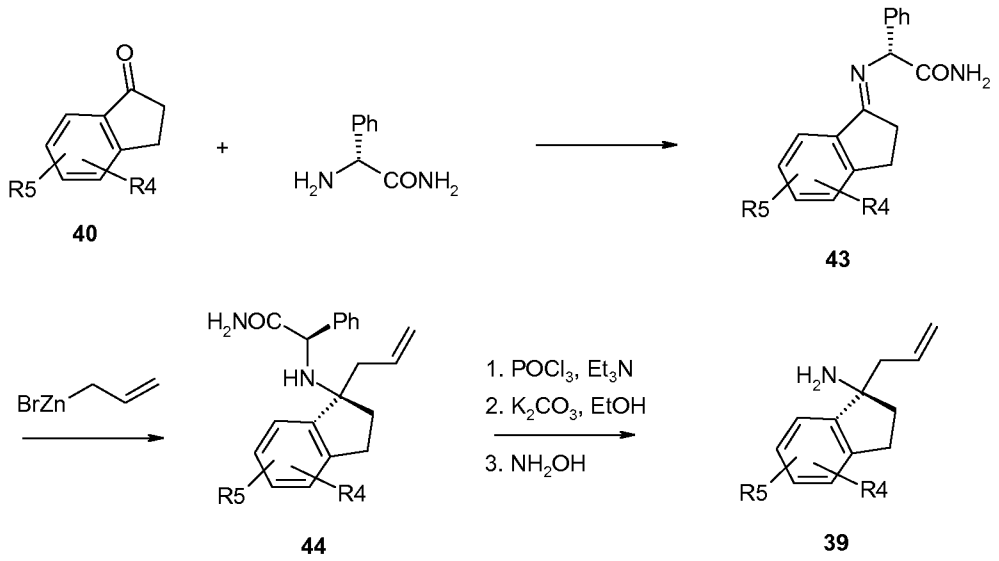
As shown in scheme 17, the required tert-butoxycarbonyl-protected allyl amines of the formula 39* are obtained by protection of the allyl amines 39 with di-tert-butyl dicarbonate using standard reaction techniques. The allyl amines 39 are accessible e.g. by a sequence of Grignard-addition of allylmagnesium bromide to acyl hydrazones (see e.g. C. Paulmier et al., Tetrahedron 2001, 57, 10259-10270), like the benzoyl hydrazones 41, derived from corresponding 1-indanones 40 and subsequent reductive cleavage of the resulting hydrazines 12. The cleavage of the hydrazines 42 by reduction to give allyl amines 39 is preferentially carried out with lithium in ammonia (see e.g. J.L. Leighton, J. Am. Chem. Soc. 2003, 125, 9596-9597) or any other method known in literature.

Scheme 17



If enantiomerically pure ß-amino ester derivatives 34 are desired, the synthesis follows the same route, starting from corresponding enatiomerically pure precursor allyl amines of the formula 39. As shown in scheme 18, the required enantiomerically pure allyl amines 39 are prepared in analogy to a procedure known from literature (Q.B. Broxterman et al., Tetrahedron: Asym. 2003, 14, 3479-3485 and Org. Lett. 2001, 3, 3943-3946). Starting either from enantiomerically pure (2*R*)- or (2*S*)-2-amino-2-phenylacetamide and 1-indanones, the corresponding imines 43 are prepared and reacted with allylzinc bromide to give either (2*R*,1*R*)- or (2*S*,1*S*)-inden-1-ylamino-2-phenylacetamides of formula 44. From the compounds of formula 44, the allyl amines of formula 39 are then obtained by a three-step sequence of dehydration, elimination and hydrolysis described in the literature (Q.B. Broxterman et al., Org. Lett. 2001, 3, 3943-3946). In scheme 18 for example, a reaction sequence starting from (2*R*)-2-amino-2-phenylacetamide to give (1*R*)-1-allylindan-1-amines is shown.

Scheme 18



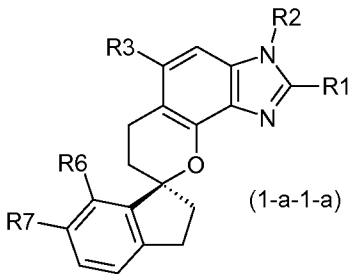
The derivatization, if any, of the compounds obtained according to the schemes above (e.g. conversion of a group R3 into another group R3 or conversion of a hydroxyl group into an alkoxy or ester group) is likewise carried out in a manner known per se. If, for example, compounds of the formula 1 where R3 = -CO-NR31R32 are desired, an appropriate derivatization can be performed in a manner known per se (e. g. conversion of an ester or a carboxylic acid into an amide), preferably at the stage of compounds of the formula 1 or at the stage of any intermediate thereof.

The reaction steps outlined above are carried out in a manner known per se, e.g. as described in more detail in the examples.

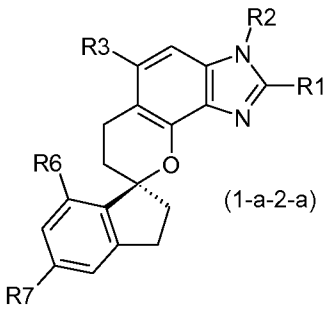
The person skilled in the art knows on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes for compounds according to this invention. All synthesis routes described herein as well as all other possible synthesis routes are also part of this invention.

The compounds of the formula 1 have, depending on the substitution, a center of chirality. The compounds of aspect a and aspect c have a center of chirality already in the basic structure, whereas in compounds of aspect b, the presence of a center of chirality depends on the position and type of substituents R6 and R7. The invention thus relates to all feasible stereoisomers in any desired mixing ratio to another, including the pure stereoisomers, which are a preferred subject of the invention.

The invention therefore particularly relates to all of the following stereoisomers of the formula 1-a-1-a, 1-a-2-a, 1-a-3-a, 1-a-4-a, 1-a-5-a, 1-a-6-a, 1-a-1-b, 1-a-2-b, 1-a-3-b, 1-a-4-b, 1-a-5-b, 1-a-6-b, 1-b-1-a, 1-b-2-a, 1-b-3-a, 1-b-4-a, 1-b-1-b, 1-b-2-b, 1-b-3-b, 1-b-4-b, 1-c-1-a, 1-c-2-a, 1-c-3-a, 1-c-4-a, 1-c-5-a, 1-c-6-a, 1-c-1-b, 1-c-2-b, 1-c-3-b, 1-c-4-b, 1-c-5-b and 1-c-6-b:



(1-a-1-a)



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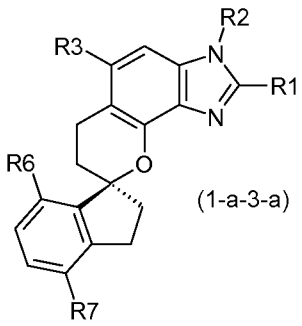

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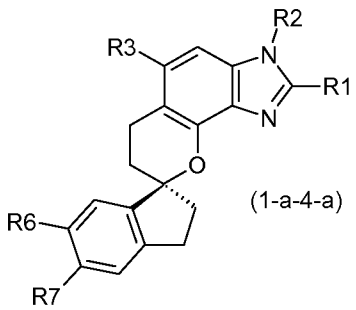

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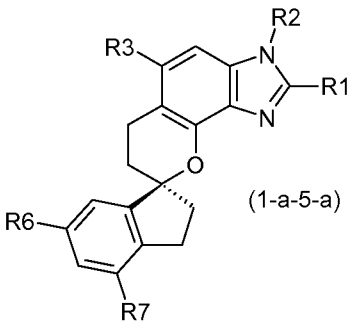

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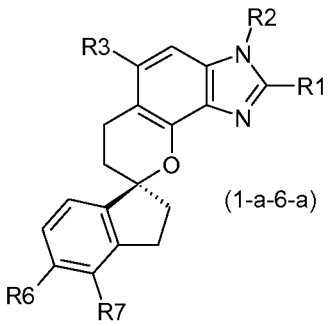

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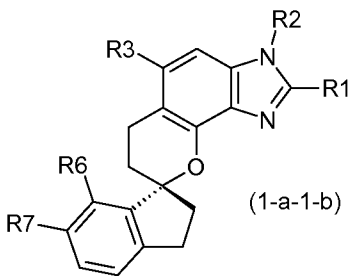

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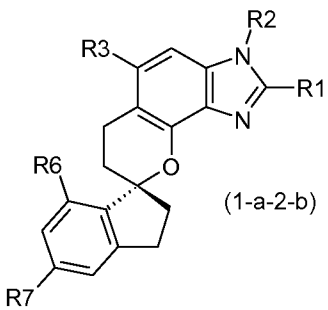

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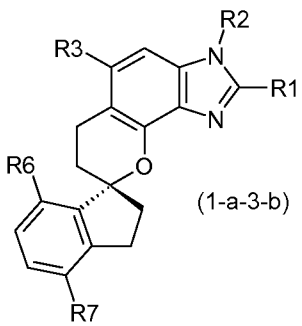

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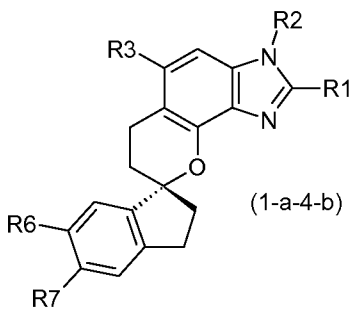

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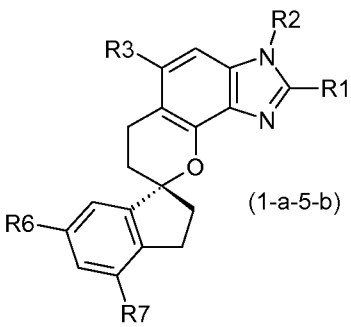

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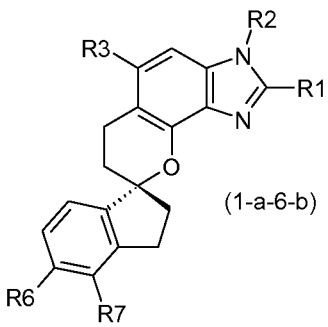

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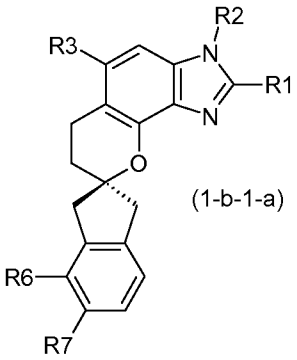

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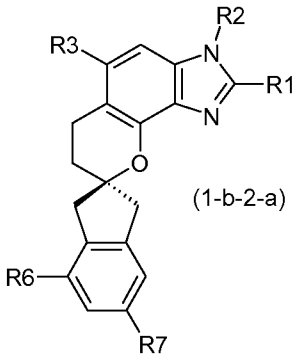

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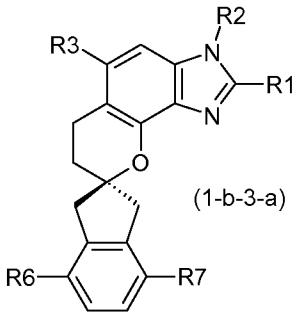

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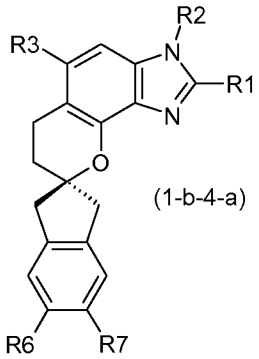

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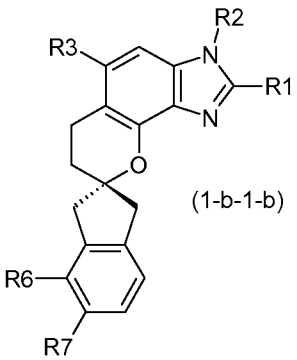

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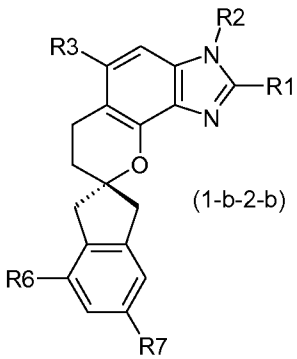

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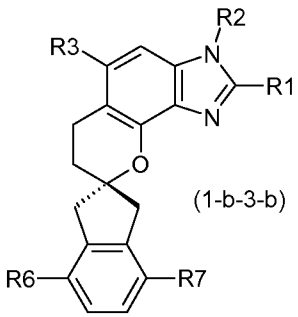

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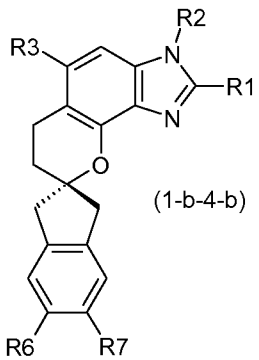

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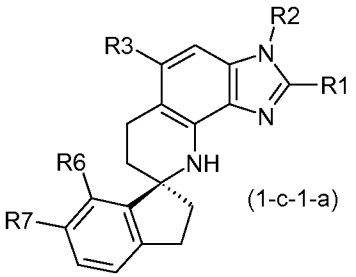
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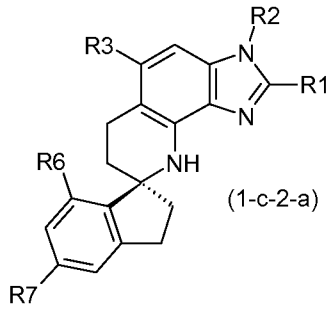
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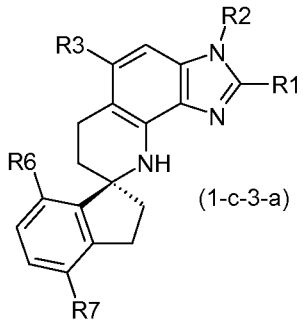
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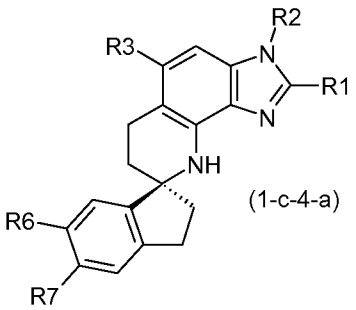
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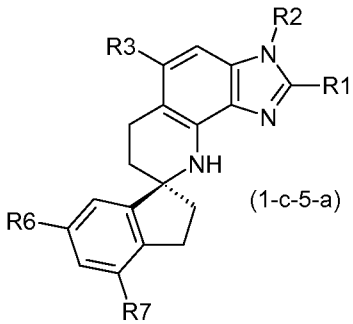
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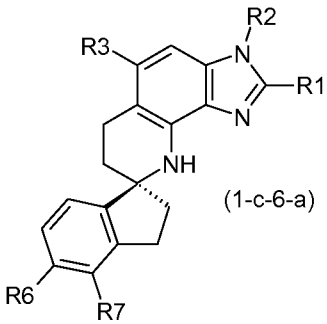
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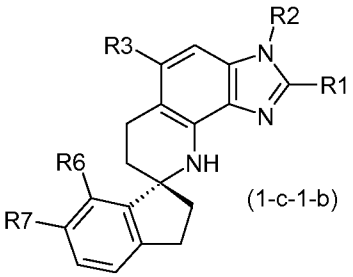
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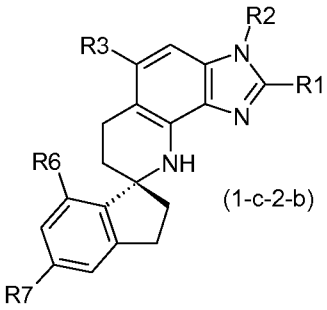
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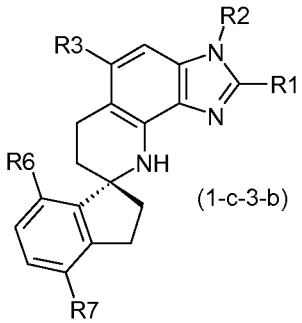
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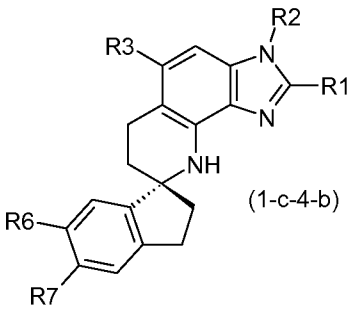
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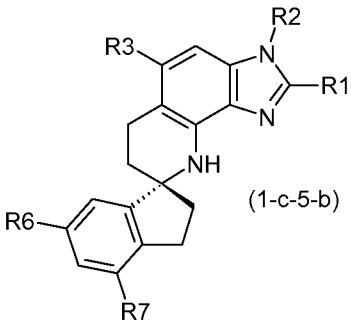
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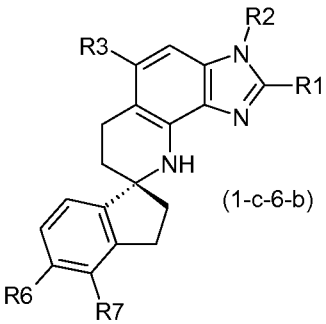

(1-c-6-b)

The pure stereoisomers of the compounds of the formula 1 and their salts according to the present invention can be obtained e.g. by asymmetric synthesis, by using chiral starting compounds in synthesis and by splitting up stereoisomeric mixtures obtained in synthesis. Preferably, the pure stereoisomers of the compounds of the formula 1 are obtained by using chiral starting compounds.

Stereoisomeric mixtures of compounds of the formula 1 can be split up into the pure stereoisomers by methods known to a person skilled in the art. Preferably, the mixtures are separated by chromatography or (fractional) crystallization. For enantiomeric mixtures the split up is preferably done by forming diastereomeric salts by adding chiral additives like chiral acids,

subsequent resolution of the salts and release of the desired compound from the salt. Alternatively, derivatization with chiral auxiliary reagents can be made, followed by diastereomer separation and removal of the chiral auxiliary group. Furthermore, enantiomeric mixtures can be separated using chiral separating columns in chromatography. Another suitable method for the separation of enantiomeric mixtures is the enzymatic separation.

Exemplary preferred compounds according to the invention are those compounds of the formula 1, wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and where X is either O or NH and R4 and R5 together form either a group G1 or a group G2, and the salts of these compounds. These compounds are either described by way of example as final products or can be prepared in an analogous manner using for example the process steps described below.

The invention therefore relates to compounds of the formula 1 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and where X is either O or NH and R4 and R5 together form either a group G1 or a group G2, and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-1 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-2 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-3 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-4 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-5 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-6 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-1 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-2 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-3 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-4 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-1 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-2 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-3 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-4 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-5 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-6 wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-1-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-2-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-3-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-4-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-5-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-6-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-1-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-2-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-3-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-4-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-5-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-a-6-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-1-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-2-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-3-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-4-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-1-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-2-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-3-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-b-4-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-1-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-2-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-3-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-4-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-5-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-6-a wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-1-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-2-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-3-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-4-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-5-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

The invention also relates to compounds of the formula 1-c-6-b wherein R1, R2, R3, R6 and R7 have the meanings as given in the following Table A (Me = CH3, Et = C2H5), and the salts of these compounds.

In the following Table A, the following definitions for the substituent R3 are used:

Amid 1 = H_2N-C(O)-

Amid 2 = CH_3-N(H)-C(O)-

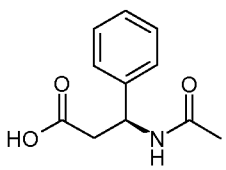
Amid 3 = $(CH_3)_2$N-C(O)-

Amid 4 = morpholino-C(O)-

Amid 5 = HO-CH_2-CH_2-N(H)-C(O)-

Amid 15 = CH_3-O-CH_2-CH_2-N(H)-C(O)-

Amid 16 = HO-CH_2-CH_2-N(CH_3)-C(O)-

Amid 17 = 

Amid 18 = cyclopropyl-CH_2-N(H)-C(O)-

Amid 19 = 3-fluoroazetidino-C(O)-

Amid 6 = 3,3-difluoro-azetidino-C(O)-

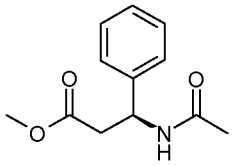
Amid 7 = CH_3-O-CH_2-CH_2-N(CH_3)-C(O)-

Amid 8 = piperidino-C(O)-

Amid 9 = cyclopropyl-N(H)-C(O)-

Amid 10 = Azetidino-C(O)-

Amid 11 = Aziridino-C(O)-

Amid 12 = 

Amid 13 = CH_3-O-N(CH_3)-C(O)-

Amid 14 = pyrrolidino-C(O)-

Amid 20 = cyclobutyl-N(H)-C(O)-

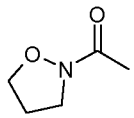
Amid 21 = CH_3-S-CH_2-CH_2-N(H)-C(O)-

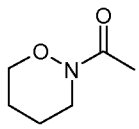
Amid 22 = CH_3-O- CH_2-CH_2-CH_2-N(H)-C(O)-

Amid 23 = CH_3-CH_2-O-CH_2-CH_2-N(H)-C(O)-

Amid 24 = CF_3-CH_2-N(H)-C(O)-

Amid 25 = 3-methoxyazetidino-C(O)-

Amid 26 = 

Amid 27 = 

Amid 28 = isobutyl-N(CH_3)-C(O)-

Amid 29 = CH_3-CH_2-N(H)-C(O)-

Amid 30 = 4-hydroxypiperidino-C(O)-

Table A

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 1	H	H		Me	H	Amid 1	H	H
Me	Me	Amid 2	H	H		Me	H	Amid 2	H	H
Me	Me	Amid 3	H	H		Me	H	Amid 3	H	H
Me	Me	Amid 4	H	H		Me	H	Amid 4	H	H
Me	Me	Amid 5	H	H		Me	H	Amid 5	H	H
Me	Me	Amid 6	H	H		Me	H	Amid 6	H	H
Me	Me	Amid 7	H	H		Me	H	Amid 7	H	H
Me	Me	Amid 8	H	H		Me	H	Amid 8	H	H
Me	Me	Amid 9	H	H		Me	H	Amid 9	H	H
Me	Me	Amid 10	H	H		Me	H	Amid 10	H	H
Me	Me	Amid 11	H	H		Me	H	Amid 11	H	H
Me	Me	Amid 12	H	H		Me	H	Amid 12	H	H
Me	Me	Amid 13	H	H		Me	H	Amid 13	H	H
Me	Me	Amid 14	H	H		Me	H	Amid 14	H	H
Me	Me	Amid 15	H	H		Me	H	Amid 15	H	H
Me	Me	Amid 16	H	H		Me	H	Amid 16	H	H
Me	Me	Amid 17	H	H		Me	H	Amid 17	H	H
Me	Me	Amid 18	H	H		Me	H	Amid 18	H	H
Me	Me	Amid 19	H	H		Me	H	Amid 19	H	H
Me	Me	Amid 20	H	H		Me	H	Amid 20	H	H
Me	Me	Amid 21	H	H		Me	H	Amid 21	H	H

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 22	H	H		Me	H	Amid 22	H	H
Me	Me	Amid 23	H	H		Me	H	Amid 23	H	H
Me	Me	Amid 24	H	H		Me	H	Amid 24	H	H
Me	Me	Amid 25	H	H		Me	H	Amid 25	H	H
Me	Me	Amid 26	H	H		Me	H	Amid 26	H	H
Me	Me	Amid 27	H	H		Me	H	Amid 27	H	H
Me	Me	Amid 28	H	H		Me	H	Amid 28	H	H
Me	Me	Amid 29	H	H		Me	H	Amid 29	H	H
Me	Me	Amid 30	H	H		Me	H	Amid 30	H	H
Me	Me	Amid 1	H	F		Me	H	Amid 1	H	F
Me	Me	Amid 2	H	F		Me	H	Amid 2	H	F
Me	Me	Amid 3	H	F		Me	H	Amid 3	H	F
Me	Me	Amid 4	H	F		Me	H	Amid 4	H	F
Me	Me	Amid 5	H	F		Me	H	Amid 5	H	F
Me	Me	Amid 6	H	F		Me	H	Amid 6	H	F
Me	Me	Amid 7	H	F		Me	H	Amid 7	H	F
Me	Me	Amid 8	H	F		Me	H	Amid 8	H	F
Me	Me	Amid 9	H	F		Me	H	Amid 9	H	F
Me	Me	Amid 10	H	F		Me	H	Amid 10	H	F
Me	Me	Amid 11	H	F		Me	H	Amid 11	H	F
Me	Me	Amid 12	H	F		Me	H	Amid 12	H	F
Me	Me	Amid 13	H	F		Me	H	Amid 13	H	F
Me	Me	Amid 14	H	F		Me	H	Amid 14	H	F
Me	Me	Amid 15	H	F		Me	H	Amid 15	H	F
Me	Me	Amid 16	H	F		Me	H	Amid 16	H	F
Me	Me	Amid 17	H	F		Me	H	Amid 17	H	F
Me	Me	Amid 18	H	F		Me	H	Amid 18	H	F
Me	Me	Amid 19	H	F		Me	H	Amid 19	H	F
Me	Me	Amid 20	H	F		Me	H	Amid 20	H	F
Me	Me	Amid 21	H	F		Me	H	Amid 21	H	F
Me	Me	Amid 22	H	F		Me	H	Amid 22	H	F
Me	Me	Amid 23	H	F		Me	H	Amid 23	H	F
Me	Me	Amid 24	H	F		Me	H	Amid 24	H	F
Me	Me	Amid 25	H	F		Me	H	Amid 25	H	F
Me	Me	Amid 26	H	F		Me	H	Amid 26	H	F
Me	Me	Amid 27	H	F		Me	H	Amid 27	H	F

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 28	H	F		Me	H	Amid 28	H	F
Me	Me	Amid 29	H	F		Me	H	Amid 29	H	F
Me	Me	Amid 30	H	F		Me	H	Amid 30	H	F
Me	Me	Amid 1	H	Cl		Me	H	Amid 1	H	Cl
Me	Me	Amid 2	H	Cl		Me	H	Amid 2	H	Cl
Me	Me	Amid 3	H	Cl		Me	H	Amid 3	H	Cl
Me	Me	Amid 4	H	Cl		Me	H	Amid 4	H	Cl
Me	Me	Amid 5	H	Cl		Me	H	Amid 5	H	Cl
Me	Me	Amid 6	H	Cl		Me	H	Amid 6	H	Cl
Me	Me	Amid 7	H	Cl		Me	H	Amid 7	H	Cl
Me	Me	Amid 8	H	Cl		Me	H	Amid 8	H	Cl
Me	Me	Amid 9	H	Cl		Me	H	Amid 9	H	Cl
Me	Me	Amid 10	H	Cl		Me	H	Amid 10	H	Cl
Me	Me	Amid 11	H	Cl		Me	H	Amid 11	H	Cl
Me	Me	Amid 12	H	Cl		Me	H	Amid 12	H	Cl
Me	Me	Amid 13	H	Cl		Me	H	Amid 13	H	Cl
Me	Me	Amid 14	H	Cl		Me	H	Amid 14	H	Cl
Me	Me	Amid 15	H	Cl		Me	H	Amid 15	H	Cl
Me	Me	Amid 16	H	Cl		Me	H	Amid 16	H	Cl
Me	Me	Amid 17	H	Cl		Me	H	Amid 17	H	Cl
Me	Me	Amid 18	H	Cl		Me	H	Amid 18	H	Cl
Me	Me	Amid 19	H	Cl		Me	H	Amid 19	H	Cl
Me	Me	Amid 20	H	Cl		Me	H	Amid 20	H	Cl
Me	Me	Amid 21	H	Cl		Me	H	Amid 21	H	Cl
Me	Me	Amid 22	H	Cl		Me	H	Amid 22	H	Cl
Me	Me	Amid 23	H	Cl		Me	H	Amid 23	H	Cl
Me	Me	Amid 24	H	Cl		Me	H	Amid 24	H	Cl
Me	Me	Amid 25	H	Cl		Me	H	Amid 25	H	Cl
Me	Me	Amid 26	H	Cl		Me	H	Amid 26	H	Cl
Me	Me	Amid 27	H	Cl		Me	H	Amid 27	H	Cl
Me	Me	Amid 28	H	Cl		Me	H	Amid 28	H	Cl
Me	Me	Amid 29	H	Cl		Me	H	Amid 29	H	Cl
Me	Me	Amid 30	H	Cl		Me	H	Amid 30	H	Cl
Me	Me	Amid 1	H	MeO		Me	H	Amid 1	H	MeO
Me	Me	Amid 2	H	MeO		Me	H	Amid 2	H	MeO

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 3	H	MeO		Me	H	Amid 3	H	MeO
Me	Me	Amid 4	H	MeO		Me	H	Amid 4	H	MeO
Me	Me	Amid 5	H	MeO		Me	H	Amid 5	H	MeO
Me	Me	Amid 6	H	MeO		Me	H	Amid 6	H	MeO
Me	Me	Amid 7	H	MeO		Me	H	Amid 7	H	MeO
Me	Me	Amid 8	H	MeO		Me	H	Amid 8	H	MeO
Me	Me	Amid 9	H	MeO		Me	H	Amid 9	H	MeO
Me	Me	Amid 10	H	MeO		Me	H	Amid 10	H	MeO
Me	Me	Amid 11	H	MeO		Me	H	Amid 11	H	MeO
Me	Me	Amid 12	H	MeO		Me	H	Amid 12	H	MeO
Me	Me	Amid 13	H	MeO		Me	H	Amid 13	H	MeO
Me	Me	Amid 14	H	MeO		Me	H	Amid 14	H	MeO
Me	Me	Amid 15	H	MeO		Me	H	Amid 15	H	MeO
Me	Me	Amid 16	H	MeO		Me	H	Amid 16	H	MeO
Me	Me	Amid 17	H	MeO		Me	H	Amid 17	H	MeO
Me	Me	Amid 18	H	MeO		Me	H	Amid 18	H	MeO
Me	Me	Amid 19	H	MeO		Me	H	Amid 19	H	MeO
Me	Me	Amid 20	H	MeO		Me	H	Amid 20	H	MeO
Me	Me	Amid 21	H	MeO		Me	H	Amid 21	H	MeO
Me	Me	Amid 22	H	MeO		Me	H	Amid 22	H	MeO
Me	Me	Amid 23	H	MeO		Me	H	Amid 23	H	MeO
Me	Me	Amid 24	H	MeO		Me	H	Amid 24	H	MeO
Me	Me	Amid 25	H	MeO		Me	H	Amid 25	H	MeO
Me	Me	Amid 26	H	MeO		Me	H	Amid 26	H	MeO
Me	Me	Amid 27	H	MeO		Me	H	Amid 27	H	MeO
Me	Me	Amid 28	H	MeO		Me	H	Amid 28	H	MeO
Me	Me	Amid 29	H	MeO		Me	H	Amid 29	H	MeO
Me	Me	Amid 30	H	MeO		Me	H	Amid 30	H	MeO
Me	Me	Amid 1	H	Me		Me	H	Amid 1	H	Me
Me	Me	Amid 2	H	Me		Me	H	Amid 2	H	Me
Me	Me	Amid 3	H	Me		Me	H	Amid 3	H	Me
Me	Me	Amid 4	H	Me		Me	H	Amid 4	H	Me
Me	Me	Amid 5	H	Me		Me	H	Amid 5	H	Me
Me	Me	Amid 6	H	Me		Me	H	Amid 6	H	Me
Me	Me	Amid 7	H	Me		Me	H	Amid 7	H	Me
Me	Me	Amid 8	H	Me		Me	H	Amid 8	H	Me

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 9	H	Me		Me	H	Amid 9	H	Me
Me	Me	Amid 10	H	Me		Me	H	Amid 10	H	Me
Me	Me	Amid 11	H	Me		Me	H	Amid 11	H	Me
Me	Me	Amid 12	H	Me		Me	H	Amid 12	H	Me
Me	Me	Amid 13	H	Me		Me	H	Amid 13	H	Me
Me	Me	Amid 14	H	Me		Me	H	Amid 14	H	Me
Me	Me	Amid 15	H	Me		Me	H	Amid 15	H	Me
Me	Me	Amid 16	H	Me		Me	H	Amid 16	H	Me
Me	Me	Amid 17	H	Me		Me	H	Amid 17	H	Me
Me	Me	Amid 18	H	Me		Me	H	Amid 18	H	Me
Me	Me	Amid 19	H	Me		Me	H	Amid 19	H	Me
Me	Me	Amid 20	H	Me		Me	H	Amid 20	H	Me
Me	Me	Amid 21	H	Me		Me	H	Amid 21	H	Me
Me	Me	Amid 22	H	Me		Me	H	Amid 22	H	Me
Me	Me	Amid 23	H	Me		Me	H	Amid 23	H	Me
Me	Me	Amid 24	H	Me		Me	H	Amid 24	H	Me
Me	Me	Amid 25	H	Me		Me	H	Amid 25	H	Me
Me	Me	Amid 26	H	Me		Me	H	Amid 26	H	Me
Me	Me	Amid 27	H	Me		Me	H	Amid 27	H	Me
Me	Me	Amid 28	H	Me		Me	H	Amid 28	H	Me
Me	Me	Amid 29	H	Me		Me	H	Amid 29	H	Me
Me	Me	Amid 30	H	Me		Me	H	Amid 30	H	Me
Me	Me	Amid 1	H	FCH_2O		Me	H	Amid 1	H	FCH_2O
Me	Me	Amid 2	H	FCH_2O		Me	H	Amid 2	H	FCH_2O
Me	Me	Amid 3	H	FCH_2O		Me	H	Amid 3	H	FCH_2O
Me	Me	Amid 4	H	FCH_2O		Me	H	Amid 4	H	FCH_2O
Me	Me	Amid 5	H	FCH_2O		Me	H	Amid 5	H	FCH_2O
Me	Me	Amid 6	H	FCH_2O		Me	H	Amid 6	H	FCH_2O
Me	Me	Amid 7	H	FCH_2O		Me	H	Amid 7	H	FCH_2O
Me	Me	Amid 8	H	FCH_2O		Me	H	Amid 8	H	FCH_2O
Me	Me	Amid 9	H	FCH_2O		Me	H	Amid 9	H	FCH_2O
Me	Me	Amid 10	H	FCH_2O		Me	H	Amid 10	H	FCH_2O
Me	Me	Amid 11	H	FCH_2O		Me	H	Amid 11	H	FCH_2O
Me	Me	Amid 12	H	FCH_2O		Me	H	Amid 12	H	FCH_2O
Me	Me	Amid 13	H	FCH_2O		Me	H	Amid 13	H	FCH_2O
Me	Me	Amid 14	H	FCH_2O		Me	H	Amid 14	H	FCH_2O

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 15	H	FCH_2O		Me	H	Amid 15	H	FCH_2O
Me	Me	Amid 16	H	FCH_2O		Me	H	Amid 16	H	FCH_2O
Me	Me	Amid 17	H	FCH_2O		Me	H	Amid 17	H	FCH_2O
Me	Me	Amid 18	H	FCH_2O		Me	H	Amid 18	H	FCH_2O
Me	Me	Amid 19	H	FCH_2O		Me	H	Amid 19	H	FCH_2O
Me	Me	Amid 20	H	FCH_2O		Me	H	Amid 20	H	FCH_2O
Me	Me	Amid 21	H	FCH_2O		Me	H	Amid 21	H	FCH_2O
Me	Me	Amid 22	H	FCH_2O		Me	H	Amid 22	H	FCH_2O
Me	Me	Amid 23	H	FCH_2O		Me	H	Amid 23	H	FCH_2O
Me	Me	Amid 24	H	FCH_2O		Me	H	Amid 24	H	FCH_2O
Me	Me	Amid 25	H	FCH_2O		Me	H	Amid 25	H	FCH_2O
Me	Me	Amid 26	H	FCH_2O		Me	H	Amid 26	H	FCH_2O
Me	Me	Amid 27	H	FCH_2O		Me	H	Amid 27	H	FCH_2O
Me	Me	Amid 28	H	FCH_2O		Me	H	Amid 28	H	FCH_2O
Me	Me	Amid 29	H	FCH_2O		Me	H	Amid 29	H	FCH_2O
Me	Me	Amid 30	H	FCH_2O		Me	H	Amid 30	H	FCH_2O
Me	Me	Amid 1	F	H		Me	H	Amid 1	F	H
Me	Me	Amid 2	F	H		Me	H	Amid 2	F	H
Me	Me	Amid 3	F	H		Me	H	Amid 3	F	H
Me	Me	Amid 4	F	H		Me	H	Amid 4	F	H
Me	Me	Amid 5	F	H		Me	H	Amid 5	F	H
Me	Me	Amid 6	F	H		Me	H	Amid 6	F	H
Me	Me	Amid 7	F	H		Me	H	Amid 7	F	H
Me	Me	Amid 8	F	H		Me	H	Amid 8	F	H
Me	Me	Amid 9	F	H		Me	H	Amid 9	F	H
Me	Me	Amid 10	F	H		Me	H	Amid 10	F	H
Me	Me	Amid 11	F	H		Me	H	Amid 11	F	H
Me	Me	Amid 12	F	H		Me	H	Amid 12	F	H
Me	Me	Amid 13	F	H		Me	H	Amid 13	F	H
Me	Me	Amid 14	F	H		Me	H	Amid 14	F	H
Me	Me	Amid 15	F	H		Me	H	Amid 15	F	H
Me	Me	Amid 16	F	H		Me	H	Amid 16	F	H
Me	Me	Amid 17	F	H		Me	H	Amid 17	F	H
Me	Me	Amid 18	F	H		Me	H	Amid 18	F	H
Me	Me	Amid 19	F	H		Me	H	Amid 19	F	H
Me	Me	Amid 20	F	H		Me	H	Amid 20	F	H

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 21	F	H		Me	H	Amid 21	F	H
Me	Me	Amid 22	F	H		Me	H	Amid 22	F	H
Me	Me	Amid 23	F	H		Me	H	Amid 23	F	H
Me	Me	Amid 24	F	H		Me	H	Amid 24	F	H
Me	Me	Amid 25	F	H		Me	H	Amid 25	F	H
Me	Me	Amid 26	F	H		Me	H	Amid 26	F	H
Me	Me	Amid 27	F	H		Me	H	Amid 27	F	H
Me	Me	Amid 28	F	H		Me	H	Amid 28	F	H
Me	Me	Amid 29	F	H		Me	H	Amid 29	F	H
Me	Me	Amid 30	F	H		Me	H	Amid 30	F	H
Me	Me	Amid 1	F	F		Me	H	Amid 1	F	F
Me	Me	Amid 2	F	F		Me	H	Amid 2	F	F
Me	Me	Amid 3	F	F		Me	H	Amid 3	F	F
Me	Me	Amid 4	F	F		Me	H	Amid 4	F	F
Me	Me	Amid 5	F	F		Me	H	Amid 5	F	F
Me	Me	Amid 6	F	F		Me	H	Amid 6	F	F
Me	Me	Amid 7	F	F		Me	H	Amid 7	F	F
Me	Me	Amid 8	F	F		Me	H	Amid 8	F	F
Me	Me	Amid 9	F	F		Me	H	Amid 9	F	F
Me	Me	Amid 10	F	F		Me	H	Amid 10	F	F
Me	Me	Amid 11	F	F		Me	H	Amid 11	F	F
Me	Me	Amid 12	F	F		Me	H	Amid 12	F	F
Me	Me	Amid 13	F	F		Me	H	Amid 13	F	F
Me	Me	Amid 14	F	F		Me	H	Amid 14	F	F
Me	Me	Amid 15	F	F		Me	H	Amid 15	F	F
Me	Me	Amid 16	F	F		Me	H	Amid 16	F	F
Me	Me	Amid 17	F	F		Me	H	Amid 17	F	F
Me	Me	Amid 18	F	F		Me	H	Amid 18	F	F
Me	Me	Amid 19	F	F		Me	H	Amid 19	F	F
Me	Me	Amid 20	F	F		Me	H	Amid 20	F	F
Me	Me	Amid 21	F	F		Me	H	Amid 21	F	F
Me	Me	Amid 22	F	F		Me	H	Amid 22	F	F
Me	Me	Amid 23	F	F		Me	H	Amid 23	F	F
Me	Me	Amid 24	F	F		Me	H	Amid 24	F	F
Me	Me	Amid 25	F	F		Me	H	Amid 25	F	F
Me	Me	Amid 26	F	F		Me	H	Amid 26	F	F

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 27	F	F		Me	H	Amid 27	F	F
Me	Me	Amid 28	F	F		Me	H	Amid 28	F	F
Me	Me	Amid 29	F	F		Me	H	Amid 29	F	F
Me	Me	Amid 1	F	Cl		Me	H	Amid 1	F	Cl
Me	Me	Amid 2	F	Cl		Me	H	Amid 2	F	Cl
Me	Me	Amid 3	F	Cl		Me	H	Amid 3	F	Cl
Me	Me	Amid 4	F	Cl		Me	H	Amid 4	F	Cl
Me	Me	Amid 5	F	Cl		Me	H	Amid 5	F	Cl
Me	Me	Amid 6	F	Cl		Me	H	Amid 6	F	Cl
Me	Me	Amid 7	F	Cl		Me	H	Amid 7	F	Cl
Me	Me	Amid 8	F	Cl		Me	H	Amid 8	F	Cl
Me	Me	Amid 9	F	Cl		Me	H	Amid 9	F	Cl
Me	Me	Amid 10	F	Cl		Me	H	Amid 10	F	Cl
Me	Me	Amid 11	F	Cl		Me	H	Amid 11	F	Cl
Me	Me	Amid 12	F	Cl		Me	H	Amid 12	F	Cl
Me	Me	Amid 13	F	Cl		Me	H	Amid 13	F	Cl
Me	Me	Amid 14	F	Cl		Me	H	Amid 14	F	Cl
Me	Me	Amid 15	F	Cl		Me	H	Amid 15	F	Cl
Me	Me	Amid 16	F	Cl		Me	H	Amid 16	F	Cl
Me	Me	Amid 17	F	Cl		Me	H	Amid 17	F	Cl
Me	Me	Amid 18	F	Cl		Me	H	Amid 18	F	Cl
Me	Me	Amid 19	F	Cl		Me	H	Amid 19	F	Cl
Me	Me	Amid 20	F	Cl		Me	H	Amid 20	F	Cl
Me	Me	Amid 21	F	Cl		Me	H	Amid 21	F	Cl
Me	Me	Amid 22	F	Cl		Me	H	Amid 22	F	Cl
Me	Me	Amid 23	F	Cl		Me	H	Amid 23	F	Cl
Me	Me	Amid 24	F	Cl		Me	H	Amid 24	F	Cl
Me	Me	Amid 25	F	Cl		Me	H	Amid 25	F	Cl
Me	Me	Amid 26	F	Cl		Me	H	Amid 26	F	Cl
Me	Me	Amid 27	F	Cl		Me	H	Amid 27	F	Cl
Me	Me	Amid 28	F	Cl		Me	H	Amid 28	F	Cl
Me	Me	Amid 29	F	Cl		Me	H	Amid 29	F	Cl
Me	Me	Amid 30	F	Cl		Me	H	Amid 30	F	Cl
Me	Me	Amid 1	F	MeO		Me	H	Amid 1	F	MeO
Me	Me	Amid 2	F	MeO		Me	H	Amid 2	F	MeO

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 3	F	MeO		Me	H	Amid 3	F	MeO
Me	Me	Amid 4	F	MeO		Me	H	Amid 4	F	MeO
Me	Me	Amid 5	F	MeO		Me	H	Amid 5	F	MeO
Me	Me	Amid 6	F	MeO		Me	H	Amid 6	F	MeO
Me	Me	Amid 7	F	MeO		Me	H	Amid 7	F	MeO
Me	Me	Amid 8	F	MeO		Me	H	Amid 8	F	MeO
Me	Me	Amid 9	F	MeO		Me	H	Amid 9	F	MeO
Me	Me	Amid 10	F	MeO		Me	H	Amid 10	F	MeO
Me	Me	Amid 11	F	MeO		Me	H	Amid 11	F	MeO
Me	Me	Amid 12	F	MeO		Me	H	Amid 12	F	MeO
Me	Me	Amid 13	F	MeO		Me	H	Amid 13	F	MeO
Me	Me	Amid 14	F	MeO		Me	H	Amid 14	F	MeO
Me	Me	Amid 15	F	MeO		Me	H	Amid 15	F	MeO
Me	Me	Amid 16	F	MeO		Me	H	Amid 16	F	MeO
Me	Me	Amid 17	F	MeO		Me	H	Amid 17	F	MeO
Me	Me	Amid 18	F	MeO		Me	H	Amid 18	F	MeO
Me	Me	Amid 19	F	MeO		Me	H	Amid 19	F	MeO
Me	Me	Amid 20	F	MeO		Me	H	Amid 20	F	MeO
Me	Me	Amid 21	F	MeO		Me	H	Amid 21	F	MeO
Me	Me	Amid 22	F	MeO		Me	H	Amid 22	F	MeO
Me	Me	Amid 23	F	MeO		Me	H	Amid 23	F	MeO
Me	Me	Amid 24	F	MeO		Me	H	Amid 24	F	MeO
Me	Me	Amid 25	F	MeO		Me	H	Amid 25	F	MeO
Me	Me	Amid 26	F	MeO		Me	H	Amid 26	F	MeO
Me	Me	Amid 27	F	MeO		Me	H	Amid 27	F	MeO
Me	Me	Amid 28	F	MeO		Me	H	Amid 28	F	MeO
Me	Me	Amid 29	F	MeO		Me	H	Amid 29	F	MeO
Me	Me	Amid 30	F	MeO		Me	H	Amid 30	F	MeO
Me	Me	Amid 1	F	Me		Me	H	Amid 1	F	Me
Me	Me	Amid 2	F	Me		Me	H	Amid 2	F	Me
Me	Me	Amid 3	F	Me		Me	H	Amid 3	F	Me
Me	Me	Amid 4	F	Me		Me	H	Amid 4	F	Me
Me	Me	Amid 5	F	Me		Me	H	Amid 5	F	Me
Me	Me	Amid 6	F	Me		Me	H	Amid 6	F	Me
Me	Me	Amid 7	F	Me		Me	H	Amid 7	F	Me
Me	Me	Amid 8	F	Me		Me	H	Amid 8	F	Me

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 9	F	Me		Me	H	Amid 9	F	Me
Me	Me	Amid 10	F	Me		Me	H	Amid 10	F	Me
Me	Me	Amid 11	F	Me		Me	H	Amid 11	F	Me
Me	Me	Amid 12	F	Me		Me	H	Amid 12	F	Me
Me	Me	Amid 13	F	Me		Me	H	Amid 13	F	Me
Me	Me	Amid 14	F	Me		Me	H	Amid 14	F	Me
Me	Me	Amid 15	F	Me		Me	H	Amid 15	F	Me
Me	Me	Amid 16	F	Me		Me	H	Amid 16	F	Me
Me	Me	Amid 17	F	Me		Me	H	Amid 17	F	Me
Me	Me	Amid 18	F	Me		Me	H	Amid 18	F	Me
Me	Me	Amid 19	F	Me		Me	H	Amid 19	F	Me
Me	Me	Amid 20	F	Me		Me	H	Amid 20	F	Me
Me	Me	Amid 21	F	Me		Me	H	Amid 21	F	Me
Me	Me	Amid 22	F	Me		Me	H	Amid 22	F	Me
Me	Me	Amid 23	F	Me		Me	H	Amid 23	F	Me
Me	Me	Amid 24	F	Me		Me	H	Amid 24	F	Me
Me	Me	Amid 25	F	Me		Me	H	Amid 25	F	Me
Me	Me	Amid 26	F	Me		Me	H	Amid 26	F	Me
Me	Me	Amid 27	F	Me		Me	H	Amid 27	F	Me
Me	Me	Amid 28	F	Me		Me	H	Amid 28	F	Me
Me	Me	Amid 29	F	Me		Me	H	Amid 29	F	Me
Me	Me	Amid 30	F	Me		Me	H	Amid 30	F	Me
Me	Me	Amid 1	F	FCH_2O		Me	H	Amid 1	F	FCH_2O
Me	Me	Amid 2	F	FCH_2O		Me	H	Amid 2	F	FCH_2O
Me	Me	Amid 3	F	FCH_2O		Me	H	Amid 3	F	FCH_2O
Me	Me	Amid 4	F	FCH_2O		Me	H	Amid 4	F	FCH_2O
Me	Me	Amid 5	F	FCH_2O		Me	H	Amid 5	F	FCH_2O
Me	Me	Amid 6	F	FCH_2O		Me	H	Amid 6	F	FCH_2O
Me	Me	Amid 7	F	FCH_2O		Me	H	Amid 7	F	FCH_2O
Me	Me	Amid 8	F	FCH_2O		Me	H	Amid 8	F	FCH_2O
Me	Me	Amid 9	F	FCH_2O		Me	H	Amid 9	F	FCH_2O
Me	Me	Amid 10	F	FCH_2O		Me	H	Amid 10	F	FCH_2O
Me	Me	Amid 11	F	FCH_2O		Me	H	Amid 11	F	FCH_2O
Me	Me	Amid 12	F	FCH_2O		Me	H	Amid 12	F	FCH_2O
Me	Me	Amid 13	F	FCH_2O		Me	H	Amid 13	F	FCH_2O
Me	Me	Amid 14	F	FCH_2O		Me	H	Amid 14	F	FCH_2O

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 15	F	FCH_2O		Me	H	Amid 15	F	FCH_2O
Me	Me	Amid 16	F	FCH_2O		Me	H	Amid 16	F	FCH_2O
Me	Me	Amid 17	F	FCH_2O		Me	H	Amid 17	F	FCH_2O
Me	Me	Amid 18	F	FCH_2O		Me	H	Amid 18	F	FCH_2O
Me	Me	Amid 19	F	FCH_2O		Me	H	Amid 19	F	FCH_2O
Me	Me	Amid 20	F	FCH_2O		Me	H	Amid 20	F	FCH_2O
Me	Me	Amid 21	F	FCH_2O		Me	H	Amid 21	F	FCH_2O
Me	Me	Amid 22	F	FCH_2O		Me	H	Amid 22	F	FCH_2O
Me	Me	Amid 23	F	FCH_2O		Me	H	Amid 23	F	FCH_2O
Me	Me	Amid 24	F	FCH_2O		Me	H	Amid 24	F	FCH_2O
Me	Me	Amid 25	F	FCH_2O		Me	H	Amid 25	F	FCH_2O
Me	Me	Amid 26	F	FCH_2O		Me	H	Amid 26	F	FCH_2O
Me	Me	Amid 27	F	FCH_2O		Me	H	Amid 27	F	FCH_2O
Me	Me	Amid 28	F	FCH_2O		Me	H	Amid 28	F	FCH_2O
Me	Me	Amid 29	F	FCH_2O		Me	H	Amid 29	F	FCH_2O
Me	Me	Amid 30	F	FCH_2O		Me	H	Amid 30	F	FCH_2O
Me	Me	Amid 1	Cl	H		Me	H	Amid 1	Cl	H
Me	Me	Amid 2	Cl	H		Me	H	Amid 2	Cl	H
Me	Me	Amid 3	Cl	H		Me	H	Amid 3	Cl	H
Me	Me	Amid 4	Cl	H		Me	H	Amid 4	Cl	H
Me	Me	Amid 5	Cl	H		Me	H	Amid 5	Cl	H
Me	Me	Amid 6	Cl	H		Me	H	Amid 6	Cl	H
Me	Me	Amid 7	Cl	H		Me	H	Amid 7	Cl	H
Me	Me	Amid 8	Cl	H		Me	H	Amid 8	Cl	H
Me	Me	Amid 9	Cl	H		Me	H	Amid 9	Cl	H
Me	Me	Amid 10	Cl	H		Me	H	Amid 10	Cl	H
Me	Me	Amid 11	Cl	H		Me	H	Amid 11	Cl	H
Me	Me	Amid 12	Cl	H		Me	H	Amid 12	Cl	H
Me	Me	Amid 13	Cl	H		Me	H	Amid 13	Cl	H
Me	Me	Amid 14	Cl	H		Me	H	Amid 14	Cl	H
Me	Me	Amid 15	Cl	H		Me	H	Amid 15	Cl	H
Me	Me	Amid 16	Cl	H		Me	H	Amid 16	Cl	H
Me	Me	Amid 17	Cl	H		Me	H	Amid 17	Cl	H
Me	Me	Amid 18	Cl	H		Me	H	Amid 18	Cl	H
Me	Me	Amid 19	Cl	H		Me	H	Amid 19	Cl	H
Me	Me	Amid 20	Cl	H		Me	H	Amid 20	Cl	H

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 21	Cl	H		Me	H	Amid 21	Cl	H
Me	Me	Amid 22	Cl	H		Me	H	Amid 22	Cl	H
Me	Me	Amid 23	Cl	H		Me	H	Amid 23	Cl	H
Me	Me	Amid 24	Cl	H		Me	H	Amid 24	Cl	H
Me	Me	Amid 25	Cl	H		Me	H	Amid 25	Cl	H
Me	Me	Amid 26	Cl	H		Me	H	Amid 26	Cl	H
Me	Me	Amid 27	Cl	H		Me	H	Amid 27	Cl	H
Me	Me	Amid 28	Cl	H		Me	H	Amid 28	Cl	H
Me	Me	Amid 29	Cl	H		Me	H	Amid 29	Cl	H
Me	Me	Amid 30	Cl	H		Me	H	Amid 30	Cl	H
Me	Me	Amid 1	Cl	F		Me	H	Amid 1	Cl	F
Me	Me	Amid 2	Cl	F		Me	H	Amid 2	Cl	F
Me	Me	Amid 3	Cl	F		Me	H	Amid 3	Cl	F
Me	Me	Amid 4	Cl	F		Me	H	Amid 4	Cl	F
Me	Me	Amid 5	Cl	F		Me	H	Amid 5	Cl	F
Me	Me	Amid 6	Cl	F		Me	H	Amid 6	Cl	F
Me	Me	Amid 7	Cl	F		Me	H	Amid 7	Cl	F
Me	Me	Amid 8	Cl	F		Me	H	Amid 8	Cl	F
Me	Me	Amid 9	Cl	F		Me	H	Amid 9	Cl	F
Me	Me	Amid 10	Cl	F		Me	H	Amid 10	Cl	F
Me	Me	Amid 11	Cl	F		Me	H	Amid 11	Cl	F
Me	Me	Amid 12	Cl	F		Me	H	Amid 12	Cl	F
Me	Me	Amid 13	Cl	F		Me	H	Amid 13	Cl	F
Me	Me	Amid 14	Cl	F		Me	H	Amid 14	Cl	F
Me	Me	Amid 15	Cl	F		Me	H	Amid 15	Cl	F
Me	Me	Amid 16	Cl	F		Me	H	Amid 16	Cl	F
Me	Me	Amid 17	Cl	F		Me	H	Amid 17	Cl	F
Me	Me	Amid 18	Cl	F		Me	H	Amid 18	Cl	F
Me	Me	Amid 19	Cl	F		Me	H	Amid 19	Cl	F
Me	Me	Amid 20	Cl	F		Me	H	Amid 20	Cl	F
Me	Me	Amid 21	Cl	F		Me	H	Amid 21	Cl	F
Me	Me	Amid 22	Cl	F		Me	H	Amid 22	Cl	F
Me	Me	Amid 23	Cl	F		Me	H	Amid 23	Cl	F
Me	Me	Amid 24	Cl	F		Me	H	Amid 24	Cl	F
Me	Me	Amid 25	Cl	F		Me	H	Amid 25	Cl	F
Me	Me	Amid 26	Cl	F		Me	H	Amid 26	Cl	F

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 27	Cl	F		Me	H	Amid 27	Cl	F
Me	Me	Amid 28	Cl	F		Me	H	Amid 28	Cl	F
Me	Me	Amid 29	Cl	F		Me	H	Amid 29	Cl	F
Me	Me	Amid 30	Cl	F		Me	H	Amid 30	Cl	F
Me	Me	Amid 1	Cl	Cl		Me	H	Amid 1	Cl	Cl
Me	Me	Amid 2	Cl	Cl		Me	H	Amid 2	Cl	Cl
Me	Me	Amid 3	Cl	Cl		Me	H	Amid 3	Cl	Cl
Me	Me	Amid 4	Cl	Cl		Me	H	Amid 4	Cl	Cl
Me	Me	Amid 5	Cl	Cl		Me	H	Amid 5	Cl	Cl
Me	Me	Amid 6	Cl	Cl		Me	H	Amid 6	Cl	Cl
Me	Me	Amid 7	Cl	Cl		Me	H	Amid 7	Cl	Cl
Me	Me	Amid 8	Cl	Cl		Me	H	Amid 8	Cl	Cl
Me	Me	Amid 9	Cl	Cl		Me	H	Amid 9	Cl	Cl
Me	Me	Amid 10	Cl	Cl		Me	H	Amid 10	Cl	Cl
Me	Me	Amid 11	Cl	Cl		Me	H	Amid 11	Cl	Cl
Me	Me	Amid 12	Cl	Cl		Me	H	Amid 12	Cl	Cl
Me	Me	Amid 13	Cl	Cl		Me	H	Amid 13	Cl	Cl
Me	Me	Amid 14	Cl	Cl		Me	H	Amid 14	Cl	Cl
Me	Me	Amid 15	Cl	Cl		Me	H	Amid 15	Cl	Cl
Me	Me	Amid 16	Cl	Cl		Me	H	Amid 16	Cl	Cl
Me	Me	Amid 17	Cl	Cl		Me	H	Amid 17	Cl	Cl
Me	Me	Amid 18	Cl	Cl		Me	H	Amid 18	Cl	Cl
Me	Me	Amid 19	Cl	Cl		Me	H	Amid 19	Cl	Cl
Me	Me	Amid 20	Cl	Cl		Me	H	Amid 20	Cl	Cl
Me	Me	Amid 21	Cl	Cl		Me	H	Amid 21	Cl	Cl
Me	Me	Amid 22	Cl	Cl		Me	H	Amid 22	Cl	Cl
Me	Me	Amid 23	Cl	Cl		Me	H	Amid 23	Cl	Cl
Me	Me	Amid 24	Cl	Cl		Me	H	Amid 24	Cl	Cl
Me	Me	Amid 25	Cl	Cl		Me	H	Amid 25	Cl	Cl
Me	Me	Amid 26	Cl	Cl		Me	H	Amid 26	Cl	Cl
Me	Me	Amid 27	Cl	Cl		Me	H	Amid 27	Cl	Cl
Me	Me	Amid 28	Cl	Cl		Me	H	Amid 28	Cl	Cl
Me	Me	Amid 29	Cl	Cl		Me	H	Amid 29	Cl	Cl
Me	Me	Amid 30	Cl	Cl		Me	H	Amid 30	Cl	Cl
Me	Me	Amid 1	Cl	MeO		Me	H	Amid 1	Cl	MeO

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 2	Cl	MeO		Me	H	Amid 2	Cl	MeO
Me	Me	Amid 3	Cl	MeO		Me	H	Amid 3	Cl	MeO
Me	Me	Amid 4	Cl	MeO		Me	H	Amid 4	Cl	MeO
Me	Me	Amid 5	Cl	MeO		Me	H	Amid 5	Cl	MeO
Me	Me	Amid 6	Cl	MeO		Me	H	Amid 6	Cl	MeO
Me	Me	Amid 7	Cl	MeO		Me	H	Amid 7	Cl	MeO
Me	Me	Amid 8	Cl	MeO		Me	H	Amid 8	Cl	MeO
Me	Me	Amid 9	Cl	MeO		Me	H	Amid 9	Cl	MeO
Me	Me	Amid 10	Cl	MeO		Me	H	Amid 10	Cl	MeO
Me	Me	Amid 11	Cl	MeO		Me	H	Amid 11	Cl	MeO
Me	Me	Amid 12	Cl	MeO		Me	H	Amid 12	Cl	MeO
Me	Me	Amid 13	Cl	MeO		Me	H	Amid 13	Cl	MeO
Me	Me	Amid 14	Cl	MeO		Me	H	Amid 14	Cl	MeO
Me	Me	Amid 15	Cl	MeO		Me	H	Amid 15	Cl	MeO
Me	Me	Amid 16	Cl	MeO		Me	H	Amid 16	Cl	MeO
Me	Me	Amid 17	Cl	MeO		Me	H	Amid 17	Cl	MeO
Me	Me	Amid 18	Cl	MeO		Me	H	Amid 18	Cl	MeO
Me	Me	Amid 19	Cl	MeO		Me	H	Amid 19	Cl	MeO
Me	Me	Amid 20	Cl	MeO		Me	H	Amid 20	Cl	MeO
Me	Me	Amid 21	Cl	MeO		Me	H	Amid 21	Cl	MeO
Me	Me	Amid 22	Cl	MeO		Me	H	Amid 22	Cl	MeO
Me	Me	Amid 23	Cl	MeO		Me	H	Amid 23	Cl	MeO
Me	Me	Amid 24	Cl	MeO		Me	H	Amid 24	Cl	MeO
Me	Me	Amid 25	Cl	MeO		Me	H	Amid 25	Cl	MeO
Me	Me	Amid 26	Cl	MeO		Me	H	Amid 26	Cl	MeO
Me	Me	Amid 27	Cl	MeO		Me	H	Amid 27	Cl	MeO
Me	Me	Amid 28	Cl	MeO		Me	H	Amid 28	Cl	MeO
Me	Me	Amid 29	Cl	MeO		Me	H	Amid 29	Cl	MeO
Me	Me	Amid 30	Cl	MeO		Me	H	Amid 30	Cl	MeO
Me	Me	Amid 1	Cl	Me		Me	H	Amid 1	Cl	Me
Me	Me	Amid 2	Cl	Me		Me	H	Amid 2	Cl	Me
Me	Me	Amid 3	Cl	Me		Me	H	Amid 3	Cl	Me
Me	Me	Amid 4	Cl	Me		Me	H	Amid 4	Cl	Me
Me	Me	Amid 5	Cl	Me		Me	H	Amid 5	Cl	Me
Me	Me	Amid 6	Cl	Me		Me	H	Amid 6	Cl	Me
Me	Me	Amid 7	Cl	Me		Me	H	Amid 7	Cl	Me

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 8	Cl	Me		Me	H	Amid 8	Cl	Me
Me	Me	Amid 9	Cl	Me		Me	H	Amid 9	Cl	Me
Me	Me	Amid 10	Cl	Me		Me	H	Amid 10	Cl	Me
Me	Me	Amid 11	Cl	Me		Me	H	Amid 11	Cl	Me
Me	Me	Amid 12	Cl	Me		Me	H	Amid 12	Cl	Me
Me	Me	Amid 13	Cl	Me		Me	H	Amid 13	Cl	Me
Me	Me	Amid 14	Cl	Me		Me	H	Amid 14	Cl	Me
Me	Me	Amid 15	Cl	Me		Me	H	Amid 15	Cl	Me
Me	Me	Amid 16	Cl	Me		Me	H	Amid 16	Cl	Me
Me	Me	Amid 17	Cl	Me		Me	H	Amid 17	Cl	Me
Me	Me	Amid 18	Cl	Me		Me	H	Amid 18	Cl	Me
Me	Me	Amid 19	Cl	Me		Me	H	Amid 19	Cl	Me
Me	Me	Amid 20	Cl	Me		Me	H	Amid 20	Cl	Me
Me	Me	Amid 21	Cl	Me		Me	H	Amid 21	Cl	Me
Me	Me	Amid 22	Cl	Me		Me	H	Amid 22	Cl	Me
Me	Me	Amid 23	Cl	Me		Me	H	Amid 23	Cl	Me
Me	Me	Amid 24	Cl	Me		Me	H	Amid 24	Cl	Me
Me	Me	Amid 25	Cl	Me		Me	H	Amid 25	Cl	Me
Me	Me	Amid 26	Cl	Me		Me	H	Amid 26	Cl	Me
Me	Me	Amid 27	Cl	Me		Me	H	Amid 27	Cl	Me
Me	Me	Amid 28	Cl	Me		Me	H	Amid 28	Cl	Me
Me	Me	Amid 29	Cl	Me		Me	H	Amid 29	Cl	Me
Me	Me	Amid 30	Cl	Me		Me	H	Amid 30	Cl	Me
Me	Me	Amid 1	Cl	FCH_2O		Me	H	Amid 1	Cl	FCH_2O
Me	Me	Amid 2	Cl	FCH_2O		Me	H	Amid 2	Cl	FCH_2O
Me	Me	Amid 3	Cl	FCH_2O		Me	H	Amid 3	Cl	FCH_2O
Me	Me	Amid 4	Cl	FCH_2O		Me	H	Amid 4	Cl	FCH_2O
Me	Me	Amid 5	Cl	FCH_2O		Me	H	Amid 5	Cl	FCH_2O
Me	Me	Amid 6	Cl	FCH_2O		Me	H	Amid 6	Cl	FCH_2O
Me	Me	Amid 7	Cl	FCH_2O		Me	H	Amid 7	Cl	FCH_2O
Me	Me	Amid 8	Cl	FCH_2O		Me	H	Amid 8	Cl	FCH_2O
Me	Me	Amid 9	Cl	FCH_2O		Me	H	Amid 9	Cl	FCH_2O
Me	Me	Amid 10	Cl	FCH_2O		Me	H	Amid 10	Cl	FCH_2O
Me	Me	Amid 11	Cl	FCH_2O		Me	H	Amid 11	Cl	FCH_2O
Me	Me	Amid 12	Cl	FCH_2O		Me	H	Amid 12	Cl	FCH_2O
Me	Me	Amid 13	Cl	FCH_2O		Me	H	Amid 13	Cl	FCH_2O

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 14	Cl	FCH_2O		Me	H	Amid 14	Cl	FCH_2O
Me	Me	Amid 15	Cl	FCH_2O		Me	H	Amid 15	Cl	FCH_2O
Me	Me	Amid 16	Cl	FCH_2O		Me	H	Amid 16	Cl	FCH_2O
Me	Me	Amid 17	Cl	FCH_2O		Me	H	Amid 17	Cl	FCH_2O
Me	Me	Amid 18	Cl	FCH_2O		Me	H	Amid 18	Cl	FCH_2O
Me	Me	Amid 19	Cl	FCH_2O		Me	H	Amid 19	Cl	FCH_2O
Me	Me	Amid 20	Cl	FCH_2O		Me	H	Amid 20	Cl	FCH_2O
Me	Me	Amid 21	Cl	FCH_2O		Me	H	Amid 21	Cl	FCH_2O
Me	Me	Amid 22	Cl	FCH_2O		Me	H	Amid 22	Cl	FCH_2O
Me	Me	Amid 23	Cl	FCH_2O		Me	H	Amid 23	Cl	FCH_2O
Me	Me	Amid 24	Cl	FCH_2O		Me	H	Amid 24	Cl	FCH_2O
Me	Me	Amid 25	Cl	FCH_2O		Me	H	Amid 25	Cl	FCH_2O
Me	Me	Amid 26	Cl	FCH_2O		Me	H	Amid 26	Cl	FCH_2O
Me	Me	Amid 27	Cl	FCH_2O		Me	H	Amid 27	Cl	FCH_2O
Me	Me	Amid 28	Cl	FCH_2O		Me	H	Amid 28	Cl	FCH_2O
Me	Me	Amid 29	Cl	FCH_2O		Me	H	Amid 29	Cl	FCH_2O
Me	Me	Amid 30	Cl	FCH_2O		Me	H	Amid 30	Cl	FCH_2O
Me	Me	Amid 1	MeO	H		Me	H	Amid 1	MeO	H
Me	Me	Amid 2	MeO	H		Me	H	Amid 2	MeO	H
Me	Me	Amid 3	MeO	H		Me	H	Amid 3	MeO	H
Me	Me	Amid 4	MeO	H		Me	H	Amid 4	MeO	H
Me	Me	Amid 5	MeO	H		Me	H	Amid 5	MeO	H
Me	Me	Amid 6	MeO	H		Me	H	Amid 6	MeO	H
Me	Me	Amid 7	MeO	H		Me	H	Amid 7	MeO	H
Me	Me	Amid 8	MeO	H		Me	H	Amid 8	MeO	H
Me	Me	Amid 9	MeO	H		Me	H	Amid 9	MeO	H
Me	Me	Amid 10	MeO	H		Me	H	Amid 10	MeO	H
Me	Me	Amid 11	MeO	H		Me	H	Amid 11	MeO	H
Me	Me	Amid 12	MeO	H		Me	H	Amid 12	MeO	H
Me	Me	Amid 13	MeO	H		Me	H	Amid 13	MeO	H
Me	Me	Amid 14	MeO	H		Me	H	Amid 14	MeO	H
Me	Me	Amid 15	MeO	H		Me	H	Amid 15	MeO	H
Me	Me	Amid 16	MeO	H		Me	H	Amid 16	MeO	H
Me	Me	Amid 17	MeO	H		Me	H	Amid 17	MeO	H
Me	Me	Amid 18	MeO	H		Me	H	Amid 18	MeO	H
Me	Me	Amid 19	MeO	H		Me	H	Amid 19	MeO	H

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 20	MeO	H		Me	H	Amid 20	MeO	H
Me	Me	Amid 21	MeO	H		Me	H	Amid 21	MeO	H
Me	Me	Amid 22	MeO	H		Me	H	Amid 22	MeO	H
Me	Me	Amid 23	MeO	H		Me	H	Amid 23	MeO	H
Me	Me	Amid 24	MeO	H		Me	H	Amid 24	MeO	H
Me	Me	Amid 25	MeO	H		Me	H	Amid 25	MeO	H
Me	Me	Amid 26	MeO	H		Me	H	Amid 26	MeO	H
Me	Me	Amid 27	MeO	H		Me	H	Amid 27	MeO	H
Me	Me	Amid 28	MeO	H		Me	H	Amid 28	MeO	H
Me	Me	Amid 29	MeO	H		Me	H	Amid 29	MeO	H
Me	Me	Amid 30	MeO	H		Me	H	Amid 30	MeO	H
Me	Me	Amid 1	MeO	F		Me	H	Amid 1	MeO	F
Me	Me	Amid 2	MeO	F		Me	H	Amid 2	MeO	F
Me	Me	Amid 3	MeO	F		Me	H	Amid 3	MeO	F
Me	Me	Amid 4	MeO	F		Me	H	Amid 4	MeO	F
Me	Me	Amid 5	MeO	F		Me	H	Amid 5	MeO	F
Me	Me	Amid 6	MeO	F		Me	H	Amid 6	MeO	F
Me	Me	Amid 7	MeO	F		Me	H	Amid 7	MeO	F
Me	Me	Amid 8	MeO	F		Me	H	Amid 8	MeO	F
Me	Me	Amid 9	MeO	F		Me	H	Amid 9	MeO	F
Me	Me	Amid 10	MeO	F		Me	H	Amid 10	MeO	F
Me	Me	Amid 11	MeO	F		Me	H	Amid 11	MeO	F
Me	Me	Amid 12	MeO	F		Me	H	Amid 12	MeO	F
Me	Me	Amid 13	MeO	F		Me	H	Amid 13	MeO	F
Me	Me	Amid 14	MeO	F		Me	H	Amid 14	MeO	F
Me	Me	Amid 15	MeO	F		Me	H	Amid 15	MeO	F
Me	Me	Amid 16	MeO	F		Me	H	Amid 16	MeO	F
Me	Me	Amid 17	MeO	F		Me	H	Amid 17	MeO	F
Me	Me	Amid 18	MeO	F		Me	H	Amid 18	MeO	F
Me	Me	Amid 19	MeO	F		Me	H	Amid 19	MeO	F
Me	Me	Amid 20	MeO	F		Me	H	Amid 20	MeO	F
Me	Me	Amid 21	MeO	F		Me	H	Amid 21	MeO	F
Me	Me	Amid 22	MeO	F		Me	H	Amid 22	MeO	F
Me	Me	Amid 23	MeO	F		Me	H	Amid 23	MeO	F
Me	Me	Amid 24	MeO	F		Me	H	Amid 24	MeO	F
Me	Me	Amid 25	MeO	F		Me	H	Amid 25	MeO	F

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 26	MeO	F		Me	H	Amid 26	MeO	F
Me	Me	Amid 27	MeO	F		Me	H	Amid 27	MeO	F
Me	Me	Amid 28	MeO	F		Me	H	Amid 28	MeO	F
Me	Me	Amid 29	MeO	F		Me	H	Amid 29	MeO	F
Me	Me	Amid 30	MeO	F		Me	H	Amid 30	MeO	F
Me	Me	Amid 1	MeO	Cl		Me	H	Amid 1	MeO	Cl
Me	Me	Amid 2	MeO	Cl		Me	H	Amid 2	MeO	Cl
Me	Me	Amid 3	MeO	Cl		Me	H	Amid 3	MeO	Cl
Me	Me	Amid 4	MeO	Cl		Me	H	Amid 4	MeO	Cl
Me	Me	Amid 5	MeO	Cl		Me	H	Amid 5	MeO	Cl
Me	Me	Amid 6	MeO	Cl		Me	H	Amid 6	MeO	Cl
Me	Me	Amid 7	MeO	Cl		Me	H	Amid 7	MeO	Cl
Me	Me	Amid 8	MeO	Cl		Me	H	Amid 8	MeO	Cl
Me	Me	Amid 9	MeO	Cl		Me	H	Amid 9	MeO	Cl
Me	Me	Amid 10	MeO	Cl		Me	H	Amid 10	MeO	Cl
Me	Me	Amid 11	MeO	Cl		Me	H	Amid 11	MeO	Cl
Me	Me	Amid 12	MeO	Cl		Me	H	Amid 12	MeO	Cl
Me	Me	Amid 13	MeO	Cl		Me	H	Amid 13	MeO	Cl
Me	Me	Amid 14	MeO	Cl		Me	H	Amid 14	MeO	Cl
Me	Me	Amid 15	MeO	Cl		Me	H	Amid 15	MeO	Cl
Me	Me	Amid 16	MeO	Cl		Me	H	Amid 16	MeO	Cl
Me	Me	Amid 17	MeO	Cl		Me	H	Amid 17	MeO	Cl
Me	Me	Amid 18	MeO	Cl		Me	H	Amid 18	MeO	Cl
Me	Me	Amid 19	MeO	Cl		Me	H	Amid 19	MeO	Cl
Me	Me	Amid 20	MeO	Cl		Me	H	Amid 20	MeO	Cl
Me	Me	Amid 21	MeO	Cl		Me	H	Amid 21	MeO	Cl
Me	Me	Amid 22	MeO	Cl		Me	H	Amid 22	MeO	Cl
Me	Me	Amid 23	MeO	Cl		Me	H	Amid 23	MeO	Cl
Me	Me	Amid 24	MeO	Cl		Me	H	Amid 24	MeO	Cl
Me	Me	Amid 25	MeO	Cl		Me	H	Amid 25	MeO	Cl
Me	Me	Amid 26	MeO	Cl		Me	H	Amid 26	MeO	Cl
Me	Me	Amid 27	MeO	Cl		Me	H	Amid 27	MeO	Cl
Me	Me	Amid 28	MeO	Cl		Me	H	Amid 28	MeO	Cl
Me	Me	Amid 29	MeO	Cl		Me	H	Amid 29	MeO	Cl
Me	Me	Amid 30	MeO	Cl		Me	H	Amid 30	MeO	Cl

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 1	MeO	MeO		Me	H	Amid 1	MeO	MeO
Me	Me	Amid 2	MeO	MeO		Me	H	Amid 2	MeO	MeO
Me	Me	Amid 3	MeO	MeO		Me	H	Amid 3	MeO	MeO
Me	Me	Amid 4	MeO	MeO		Me	H	Amid 4	MeO	MeO
Me	Me	Amid 5	MeO	MeO		Me	H	Amid 5	MeO	MeO
Me	Me	Amid 6	MeO	MeO		Me	H	Amid 6	MeO	MeO
Me	Me	Amid 7	MeO	MeO		Me	H	Amid 7	MeO	MeO
Me	Me	Amid 8	MeO	MeO		Me	H	Amid 8	MeO	MeO
Me	Me	Amid 9	MeO	MeO		Me	H	Amid 9	MeO	MeO
Me	Me	Amid 10	MeO	MeO		Me	H	Amid 10	MeO	MeO
Me	Me	Amid 11	MeO	MeO		Me	H	Amid 11	MeO	MeO
Me	Me	Amid 12	MeO	MeO		Me	H	Amid 12	MeO	MeO
Me	Me	Amid 13	MeO	MeO		Me	H	Amid 13	MeO	MeO
Me	Me	Amid 14	MeO	MeO		Me	H	Amid 14	MeO	MeO
Me	Me	Amid 15	MeO	MeO		Me	H	Amid 15	MeO	MeO
Me	Me	Amid 16	MeO	MeO		Me	H	Amid 16	MeO	MeO
Me	Me	Amid 17	MeO	MeO		Me	H	Amid 17	MeO	MeO
Me	Me	Amid 18	MeO	MeO		Me	H	Amid 18	MeO	MeO
Me	Me	Amid 19	MeO	MeO		Me	H	Amid 19	MeO	MeO
Me	Me	Amid 20	MeO	MeO		Me	H	Amid 20	MeO	MeO
Me	Me	Amid 21	MeO	MeO		Me	H	Amid 21	MeO	MeO
Me	Me	Amid 22	MeO	MeO		Me	H	Amid 22	MeO	MeO
Me	Me	Amid 23	MeO	MeO		Me	H	Amid 23	MeO	MeO
Me	Me	Amid 24	MeO	MeO		Me	H	Amid 24	MeO	MeO
Me	Me	Amid 25	MeO	MeO		Me	H	Amid 25	MeO	MeO
Me	Me	Amid 26	MeO	MeO		Me	H	Amid 26	MeO	MeO
Me	Me	Amid 27	MeO	MeO		Me	H	Amid 27	MeO	MeO
Me	Me	Amid 28	MeO	MeO		Me	H	Amid 28	MeO	MeO
Me	Me	Amid 29	MeO	MeO		Me	H	Amid 29	MeO	MeO
Me	Me	Amid 30	MeO	MeO		Me	H	Amid 30	MeO	MeO
Me	Me	Amid 1	MeO	Me		Me	H	Amid 1	MeO	Me
Me	Me	Amid 2	MeO	Me		Me	H	Amid 2	MeO	Me
Me	Me	Amid 3	MeO	Me		Me	H	Amid 3	MeO	Me
Me	Me	Amid 4	MeO	Me		Me	H	Amid 4	MeO	Me
Me	Me	Amid 5	MeO	Me		Me	H	Amid 5	MeO	Me
Me	Me	Amid 6	MeO	Me		Me	H	Amid 6	MeO	Me

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 7	MeO	Me		Me	H	Amid 7	MeO	Me
Me	Me	Amid 8	MeO	Me		Me	H	Amid 8	MeO	Me
Me	Me	Amid 9	MeO	Me		Me	H	Amid 9	MeO	Me
Me	Me	Amid 10	MeO	Me		Me	H	Amid 10	MeO	Me
Me	Me	Amid 11	MeO	Me		Me	H	Amid 11	MeO	Me
Me	Me	Amid 12	MeO	Me		Me	H	Amid 12	MeO	Me
Me	Me	Amid 13	MeO	Me		Me	H	Amid 13	MeO	Me
Me	Me	Amid 14	MeO	Me		Me	H	Amid 14	MeO	Me
Me	Me	Amid 15	MeO	Me		Me	H	Amid 15	MeO	Me
Me	Me	Amid 16	MeO	Me		Me	H	Amid 16	MeO	Me
Me	Me	Amid 17	MeO	Me		Me	H	Amid 17	MeO	Me
Me	Me	Amid 18	MeO	Me		Me	H	Amid 18	MeO	Me
Me	Me	Amid 19	MeO	Me		Me	H	Amid 19	MeO	Me
Me	Me	Amid 20	MeO	Me		Me	H	Amid 20	MeO	Me
Me	Me	Amid 21	MeO	Me		Me	H	Amid 21	MeO	Me
Me	Me	Amid 22	MeO	Me		Me	H	Amid 22	MeO	Me
Me	Me	Amid 23	MeO	Me		Me	H	Amid 23	MeO	Me
Me	Me	Amid 24	MeO	Me		Me	H	Amid 24	MeO	Me
Me	Me	Amid 25	MeO	Me		Me	H	Amid 25	MeO	Me
Me	Me	Amid 26	MeO	Me		Me	H	Amid 26	MeO	Me
Me	Me	Amid 27	MeO	Me		Me	H	Amid 27	MeO	Me
Me	Me	Amid 28	MeO	Me		Me	H	Amid 28	MeO	Me
Me	Me	Amid 29	MeO	Me		Me	H	Amid 29	MeO	Me
Me	Me	Amid 30	MeO	Me		Me	H	Amid 30	MeO	Me
Me	Me	Amid 1	MeO	FCH_2O		Me	H	Amid 1	MeO	FCH_2O
Me	Me	Amid 2	MeO	FCH_2O		Me	H	Amid 2	MeO	FCH_2O
Me	Me	Amid 3	MeO	FCH_2O		Me	H	Amid 3	MeO	FCH_2O
Me	Me	Amid 4	MeO	FCH_2O		Me	H	Amid 4	MeO	FCH_2O
Me	Me	Amid 5	MeO	FCH_2O		Me	H	Amid 5	MeO	FCH_2O
Me	Me	Amid 6	MeO	FCH_2O		Me	H	Amid 6	MeO	FCH_2O
Me	Me	Amid 7	MeO	FCH_2O		Me	H	Amid 7	MeO	FCH_2O
Me	Me	Amid 8	MeO	FCH_2O		Me	H	Amid 8	MeO	FCH_2O
Me	Me	Amid 9	MeO	FCH_2O		Me	H	Amid 9	MeO	FCH_2O
Me	Me	Amid 10	MeO	FCH_2O		Me	H	Amid 10	MeO	FCH_2O
Me	Me	Amid 11	MeO	FCH_2O		Me	H	Amid 11	MeO	FCH_2O
Me	Me	Amid 12	MeO	FCH_2O		Me	H	Amid 12	MeO	FCH_2O

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 13	MeO	FCH_2O		Me	H	Amid 13	MeO	FCH_2O
Me	Me	Amid 14	MeO	FCH_2O		Me	H	Amid 14	MeO	FCH_2O
Me	Me	Amid 15	MeO	FCH_2O		Me	H	Amid 15	MeO	FCH_2O
Me	Me	Amid 16	MeO	FCH_2O		Me	H	Amid 16	MeO	FCH_2O
Me	Me	Amid 17	MeO	FCH_2O		Me	H	Amid 17	MeO	FCH_2O
Me	Me	Amid 18	MeO	FCH_2O		Me	H	Amid 18	MeO	FCH_2O
Me	Me	Amid 19	MeO	FCH_2O		Me	H	Amid 19	MeO	FCH_2O
Me	Me	Amid 20	MeO	FCH_2O		Me	H	Amid 20	MeO	FCH_2O
Me	Me	Amid 21	MeO	FCH_2O		Me	H	Amid 21	MeO	FCH_2O
Me	Me	Amid 22	MeO	FCH_2O		Me	H	Amid 22	MeO	FCH_2O
Me	Me	Amid 23	MeO	FCH_2O		Me	H	Amid 23	MeO	FCH_2O
Me	Me	Amid 24	MeO	FCH_2O		Me	H	Amid 24	MeO	FCH_2O
Me	Me	Amid 25	MeO	FCH_2O		Me	H	Amid 25	MeO	FCH_2O
Me	Me	Amid 26	MeO	FCH_2O		Me	H	Amid 26	MeO	FCH_2O
Me	Me	Amid 27	MeO	FCH_2O		Me	H	Amid 27	MeO	FCH_2O
Me	Me	Amid 28	MeO	FCH_2O		Me	H	Amid 28	MeO	FCH_2O
Me	Me	Amid 29	MeO	FCH_2O		Me	H	Amid 29	MeO	FCH_2O
Me	Me	Amid 30	MeO	FCH_2O		Me	H	Amid 30	MeO	FCH_2O
Me	Me	Amid 1	Me	H		Me	H	Amid 1	Me	H
Me	Me	Amid 2	Me	H		Me	H	Amid 2	Me	H
Me	Me	Amid 3	Me	H		Me	H	Amid 3	Me	H
Me	Me	Amid 4	Me	H		Me	H	Amid 4	Me	H
Me	Me	Amid 5	Me	H		Me	H	Amid 5	Me	H
Me	Me	Amid 6	Me	H		Me	H	Amid 6	Me	H
Me	Me	Amid 7	Me	H		Me	H	Amid 7	Me	H
Me	Me	Amid 8	Me	H		Me	H	Amid 8	Me	H
Me	Me	Amid 9	Me	H		Me	H	Amid 9	Me	H
Me	Me	Amid 10	Me	H		Me	H	Amid 10	Me	H
Me	Me	Amid 11	Me	H		Me	H	Amid 11	Me	H
Me	Me	Amid 12	Me	H		Me	H	Amid 12	Me	H
Me	Me	Amid 13	Me	H		Me	H	Amid 13	Me	H
Me	Me	Amid 14	Me	H		Me	H	Amid 14	Me	H
Me	Me	Amid 15	Me	H		Me	H	Amid 15	Me	H
Me	Me	Amid 16	Me	H		Me	H	Amid 16	Me	H
Me	Me	Amid 17	Me	H		Me	H	Amid 17	Me	H
Me	Me	Amid 18	Me	H		Me	H	Amid 18	Me	H

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 19	Me	H		Me	H	Amid 19	Me	H
Me	Me	Amid 20	Me	H		Me	H	Amid 20	Me	H
Me	Me	Amid 21	Me	H		Me	H	Amid 21	Me	H
Me	Me	Amid 22	Me	H		Me	H	Amid 22	Me	H
Me	Me	Amid 23	Me	H		Me	H	Amid 23	Me	H
Me	Me	Amid 24	Me	H		Me	H	Amid 24	Me	H
Me	Me	Amid 25	Me	H		Me	H	Amid 25	Me	H
Me	Me	Amid 26	Me	H		Me	H	Amid 26	Me	H
Me	Me	Amid 27	Me	H		Me	H	Amid 27	Me	H
Me	Me	Amid 28	Me	H		Me	H	Amid 28	Me	H
Me	Me	Amid 29	Me	H		Me	H	Amid 29	Me	H
Me	Me	Amid 30	Me	H		Me	H	Amid 30	Me	H
Me	Me	Amid 1	Me	F		Me	H	Amid 1	Me	F
Me	Me	Amid 2	Me	F		Me	H	Amid 2	Me	F
Me	Me	Amid 3	Me	F		Me	H	Amid 3	Me	F
Me	Me	Amid 4	Me	F		Me	H	Amid 4	Me	F
Me	Me	Amid 5	Me	F		Me	H	Amid 5	Me	F
Me	Me	Amid 6	Me	F		Me	H	Amid 6	Me	F
Me	Me	Amid 7	Me	F		Me	H	Amid 7	Me	F
Me	Me	Amid 8	Me	F		Me	H	Amid 8	Me	F
Me	Me	Amid 9	Me	F		Me	H	Amid 9	Me	F
Me	Me	Amid 10	Me	F		Me	H	Amid 10	Me	F
Me	Me	Amid 11	Me	F		Me	H	Amid 11	Me	F
Me	Me	Amid 12	Me	F		Me	H	Amid 12	Me	F
Me	Me	Amid 13	Me	F		Me	H	Amid 13	Me	F
Me	Me	Amid 14	Me	F		Me	H	Amid 14	Me	F
Me	Me	Amid 15	Me	F		Me	H	Amid 15	Me	F
Me	Me	Amid 16	Me	F		Me	H	Amid 16	Me	F
Me	Me	Amid 17	Me	F		Me	H	Amid 17	Me	F
Me	Me	Amid 18	Me	F		Me	H	Amid 18	Me	F
Me	Me	Amid 19	Me	F		Me	H	Amid 19	Me	F
Me	Me	Amid 20	Me	F		Me	H	Amid 20	Me	F
Me	Me	Amid 21	Me	F		Me	H	Amid 21	Me	F
Me	Me	Amid 22	Me	F		Me	H	Amid 22	Me	F
Me	Me	Amid 23	Me	F		Me	H	Amid 23	Me	F
Me	Me	Amid 24	Me	F		Me	H	Amid 24	Me	F

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 25	Me	F		Me	H	Amid 25	Me	F
Me	Me	Amid 26	Me	F		Me	H	Amid 26	Me	F
Me	Me	Amid 27	Me	F		Me	H	Amid 27	Me	F
Me	Me	Amid 28	Me	F		Me	H	Amid 28	Me	F
Me	Me	Amid 29	Me	F		Me	H	Amid 29	Me	F
Me	Me	Amid 30	Me	F		Me	H	Amid 30	Me	F
Me	Me	Amid 1	Me	Cl		Me	H	Amid 1	Me	Cl
Me	Me	Amid 2	Me	Cl		Me	H	Amid 2	Me	Cl
Me	Me	Amid 3	Me	Cl		Me	H	Amid 3	Me	Cl
Me	Me	Amid 4	Me	Cl		Me	H	Amid 4	Me	Cl
Me	Me	Amid 5	Me	Cl		Me	H	Amid 5	Me	Cl
Me	Me	Amid 6	Me	Cl		Me	H	Amid 6	Me	Cl
Me	Me	Amid 7	Me	Cl		Me	H	Amid 7	Me	Cl
Me	Me	Amid 8	Me	Cl		Me	H	Amid 8	Me	Cl
Me	Me	Amid 9	Me	Cl		Me	H	Amid 9	Me	Cl
Me	Me	Amid 10	Me	Cl		Me	H	Amid 10	Me	Cl
Me	Me	Amid 11	Me	Cl		Me	H	Amid 11	Me	Cl
Me	Me	Amid 12	Me	Cl		Me	H	Amid 12	Me	Cl
Me	Me	Amid 13	Me	Cl		Me	H	Amid 13	Me	Cl
Me	Me	Amid 14	Me	Cl		Me	H	Amid 14	Me	Cl
Me	Me	Amid 15	Me	Cl		Me	H	Amid 15	Me	Cl
Me	Me	Amid 16	Me	Cl		Me	H	Amid 16	Me	Cl
Me	Me	Amid 17	Me	Cl		Me	H	Amid 17	Me	Cl
Me	Me	Amid 18	Me	Cl		Me	H	Amid 18	Me	Cl
Me	Me	Amid 19	Me	Cl		Me	H	Amid 19	Me	Cl
Me	Me	Amid 20	Me	Cl		Me	H	Amid 20	Me	Cl
Me	Me	Amid 21	Me	Cl		Me	H	Amid 21	Me	Cl
Me	Me	Amid 22	Me	Cl		Me	H	Amid 22	Me	Cl
Me	Me	Amid 23	Me	Cl		Me	H	Amid 23	Me	Cl
Me	Me	Amid 24	Me	Cl		Me	H	Amid 24	Me	Cl
Me	Me	Amid 25	Me	Cl		Me	H	Amid 25	Me	Cl
Me	Me	Amid 26	Me	Cl		Me	H	Amid 26	Me	Cl
Me	Me	Amid 27	Me	Cl		Me	H	Amid 27	Me	Cl
Me	Me	Amid 28	Me	Cl		Me	H	Amid 28	Me	Cl
Me	Me	Amid 29	Me	Cl		Me	H	Amid 29	Me	Cl
Me	Me	Amid 30	Me	Cl		Me	H	Amid 30	Me	Cl

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 1	Me	MeO		Me	H	Amid 1	Me	MeO
Me	Me	Amid 2	Me	MeO		Me	H	Amid 2	Me	MeO
Me	Me	Amid 3	Me	MeO		Me	H	Amid 3	Me	MeO
Me	Me	Amid 4	Me	MeO		Me	H	Amid 4	Me	MeO
Me	Me	Amid 5	Me	MeO		Me	H	Amid 5	Me	MeO
Me	Me	Amid 6	Me	MeO		Me	H	Amid 6	Me	MeO
Me	Me	Amid 7	Me	MeO		Me	H	Amid 7	Me	MeO
Me	Me	Amid 8	Me	MeO		Me	H	Amid 8	Me	MeO
Me	Me	Amid 9	Me	MeO		Me	H	Amid 9	Me	MeO
Me	Me	Amid 10	Me	MeO		Me	H	Amid 10	Me	MeO
Me	Me	Amid 11	Me	MeO		Me	H	Amid 11	Me	MeO
Me	Me	Amid 12	Me	MeO		Me	H	Amid 12	Me	MeO
Me	Me	Amid 13	Me	MeO		Me	H	Amid 13	Me	MeO
Me	Me	Amid 14	Me	MeO		Me	H	Amid 14	Me	MeO
Me	Me	Amid 15	Me	MeO		Me	H	Amid 15	Me	MeO
Me	Me	Amid 16	Me	MeO		Me	H	Amid 16	Me	MeO
Me	Me	Amid 17	Me	MeO		Me	H	Amid 17	Me	MeO
Me	Me	Amid 18	Me	MeO		Me	H	Amid 18	Me	MeO
Me	Me	Amid 19	Me	MeO		Me	H	Amid 19	Me	MeO
Me	Me	Amid 20	Me	MeO		Me	H	Amid 20	Me	MeO
Me	Me	Amid 21	Me	MeO		Me	H	Amid 21	Me	MeO
Me	Me	Amid 22	Me	MeO		Me	H	Amid 22	Me	MeO
Me	Me	Amid 23	Me	MeO		Me	H	Amid 23	Me	MeO
Me	Me	Amid 24	Me	MeO		Me	H	Amid 24	Me	MeO
Me	Me	Amid 25	Me	MeO		Me	H	Amid 25	Me	MeO
Me	Me	Amid 26	Me	MeO		Me	H	Amid 26	Me	MeO
Me	Me	Amid 27	Me	MeO		Me	H	Amid 27	Me	MeO
Me	Me	Amid 28	Me	MeO		Me	H	Amid 28	Me	MeO
Me	Me	Amid 29	Me	MeO		Me	H	Amid 29	Me	MeO
Me	Me	Amid 30	Me	MeO		Me	H	Amid 30	Me	MeO
Me	Me	Amid 1	Me	Me		Me	H	Amid 1	Me	Me
Me	Me	Amid 2	Me	Me		Me	H	Amid 2	Me	Me
Me	Me	Amid 3	Me	Me		Me	H	Amid 3	Me	Me
Me	Me	Amid 4	Me	Me		Me	H	Amid 4	Me	Me
Me	Me	Amid 5	Me	Me		Me	H	Amid 5	Me	Me

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 6	Me	Me		Me	H	Amid 6	Me	Me
Me	Me	Amid 7	Me	Me		Me	H	Amid 7	Me	Me
Me	Me	Amid 8	Me	Me		Me	H	Amid 8	Me	Me
Me	Me	Amid 9	Me	Me		Me	H	Amid 9	Me	Me
Me	Me	Amid 10	Me	Me		Me	H	Amid 10	Me	Me
Me	Me	Amid 11	Me	Me		Me	H	Amid 11	Me	Me
Me	Me	Amid 12	Me	Me		Me	H	Amid 12	Me	Me
Me	Me	Amid 13	Me	Me		Me	H	Amid 13	Me	Me
Me	Me	Amid 14	Me	Me		Me	H	Amid 14	Me	Me
Me	Me	Amid 15	Me	Me		Me	H	Amid 15	Me	Me
Me	Me	Amid 16	Me	Me		Me	H	Amid 16	Me	Me
Me	Me	Amid 17	Me	Me		Me	H	Amid 17	Me	Me
Me	Me	Amid 18	Me	Me		Me	H	Amid 18	Me	Me
Me	Me	Amid 19	Me	Me		Me	H	Amid 19	Me	Me
Me	Me	Amid 20	Me	Me		Me	H	Amid 20	Me	Me
Me	Me	Amid 21	Me	Me		Me	H	Amid 21	Me	Me
Me	Me	Amid 22	Me	Me		Me	H	Amid 22	Me	Me
Me	Me	Amid 23	Me	Me		Me	H	Amid 23	Me	Me
Me	Me	Amid 24	Me	Me		Me	H	Amid 24	Me	Me
Me	Me	Amid 25	Me	Me		Me	H	Amid 25	Me	Me
Me	Me	Amid 26	Me	Me		Me	H	Amid 26	Me	Me
Me	Me	Amid 27	Me	Me		Me	H	Amid 27	Me	Me
Me	Me	Amid 28	Me	Me		Me	H	Amid 28	Me	Me
Me	Me	Amid 29	Me	Me		Me	H	Amid 29	Me	Me
Me	Me	Amid 30	Me	Me		Me	H	Amid 30	Me	Me
Me	Me	Amid 1	Me	FCH_2O		Me	H	Amid 1	Me	FCH_2O
Me	Me	Amid 2	Me	FCH_2O		Me	H	Amid 2	Me	FCH_2O
Me	Me	Amid 3	Me	FCH_2O		Me	H	Amid 3	Me	FCH_2O
Me	Me	Amid 4	Me	FCH_2O		Me	H	Amid 4	Me	FCH_2O
Me	Me	Amid 5	Me	FCH_2O		Me	H	Amid 5	Me	FCH_2O
Me	Me	Amid 6	Me	FCH_2O		Me	H	Amid 6	Me	FCH_2O
Me	Me	Amid 7	Me	FCH_2O		Me	H	Amid 7	Me	FCH_2O
Me	Me	Amid 8	Me	FCH_2O		Me	H	Amid 8	Me	FCH_2O
Me	Me	Amid 9	Me	FCH_2O		Me	H	Amid 9	Me	FCH_2O
Me	Me	Amid 10	Me	FCH_2O		Me	H	Amid 10	Me	FCH_2O
Me	Me	Amid 11	Me	FCH_2O		Me	H	Amid 11	Me	FCH_2O

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 12	Me	FCH_2O		Me	H	Amid 12	Me	FCH_2O
Me	Me	Amid 13	Me	FCH_2O		Me	H	Amid 13	Me	FCH_2O
Me	Me	Amid 14	Me	FCH_2O		Me	H	Amid 14	Me	FCH_2O
Me	Me	Amid 15	Me	FCH_2O		Me	H	Amid 15	Me	FCH_2O
Me	Me	Amid 16	Me	FCH_2O		Me	H	Amid 16	Me	FCH_2O
Me	Me	Amid 17	Me	FCH_2O		Me	H	Amid 17	Me	FCH_2O
Me	Me	Amid 18	Me	FCH_2O		Me	H	Amid 18	Me	FCH_2O
Me	Me	Amid 19	Me	FCH_2O		Me	H	Amid 19	Me	FCH_2O
Me	Me	Amid 20	Me	FCH_2O		Me	H	Amid 20	Me	FCH_2O
Me	Me	Amid 21	Me	FCH_2O		Me	H	Amid 21	Me	FCH_2O
Me	Me	Amid 22	Me	FCH_2O		Me	H	Amid 22	Me	FCH_2O
Me	Me	Amid 23	Me	FCH_2O		Me	H	Amid 23	Me	FCH_2O
Me	Me	Amid 24	Me	FCH_2O		Me	H	Amid 24	Me	FCH_2O
Me	Me	Amid 25	Me	FCH_2O		Me	H	Amid 25	Me	FCH_2O
Me	Me	Amid 26	Me	FCH_2O		Me	H	Amid 26	Me	FCH_2O
Me	Me	Amid 27	Me	FCH_2O		Me	H	Amid 27	Me	FCH_2O
Me	Me	Amid 28	Me	FCH_2O		Me	H	Amid 28	Me	FCH_2O
Me	Me	Amid 29	Me	FCH_2O		Me	H	Amid 29	Me	FCH_2O
Me	Me	Amid 30	Me	FCH_2O		Me	H	Amid 30	Me	FCH_2O
Me	Me	Amid 1	FCH_2O	H		Me	H	Amid 1	FCH_2O	H
Me	Me	Amid 2	FCH_2O	H		Me	H	Amid 2	FCH_2O	H
Me	Me	Amid 3	FCH_2O	H		Me	H	Amid 3	FCH_2O	H
Me	Me	Amid 4	FCH_2O	H		Me	H	Amid 4	FCH_2O	H
Me	Me	Amid 5	FCH_2O	H		Me	H	Amid 5	FCH_2O	H
Me	Me	Amid 6	FCH_2O	H		Me	H	Amid 6	FCH_2O	H
Me	Me	Amid 7	FCH_2O	H		Me	H	Amid 7	FCH_2O	H
Me	Me	Amid 8	FCH_2O	H		Me	H	Amid 8	FCH_2O	H
Me	Me	Amid 9	FCH_2O	H		Me	H	Amid 9	FCH_2O	H
Me	Me	Amid 10	FCH_2O	H		Me	H	Amid 10	FCH_2O	H
Me	Me	Amid 11	FCH_2O	H		Me	H	Amid 11	FCH_2O	H
Me	Me	Amid 12	FCH_2O	H		Me	H	Amid 12	FCH_2O	H
Me	Me	Amid 13	FCH_2O	H		Me	H	Amid 13	FCH_2O	H
Me	Me	Amid 14	FCH_2O	H		Me	H	Amid 14	FCH_2O	H
Me	Me	Amid 15	FCH_2O	H		Me	H	Amid 15	FCH_2O	H
Me	Me	Amid 16	FCH_2O	H		Me	H	Amid 16	FCH_2O	H
Me	Me	Amid 17	FCH_2O	H		Me	H	Amid 17	FCH_2O	H

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 18	FCH_2O	H		Me	H	Amid 18	FCH_2O	H
Me	Me	Amid 19	FCH_2O	H		Me	H	Amid 19	FCH_2O	H
Me	Me	Amid 20	FCH_2O	H		Me	H	Amid 20	FCH_2O	H
Me	Me	Amid 21	FCH_2O	H		Me	H	Amid 21	FCH_2O	H
Me	Me	Amid 22	FCH_2O	H		Me	H	Amid 22	FCH_2O	H
Me	Me	Amid 23	FCH_2O	H		Me	H	Amid 23	FCH_2O	H
Me	Me	Amid 24	FCH_2O	H		Me	H	Amid 24	FCH_2O	H
Me	Me	Amid 25	FCH_2O	H		Me	H	Amid 25	FCH_2O	H
Me	Me	Amid 26	FCH_2O	H		Me	H	Amid 26	FCH_2O	H
Me	Me	Amid 27	FCH_2O	H		Me	H	Amid 27	FCH_2O	H
Me	Me	Amid 28	FCH_2O	H		Me	H	Amid 28	FCH_2O	H
Me	Me	Amid 29	FCH_2O	H		Me	H	Amid 29	FCH_2O	H
Me	Me	Amid 30	FCH_2O	H		Me	H	Amid 30	FCH_2O	H
Me	Me	Amid 1	FCH_2O	F		Me	H	Amid 1	FCH_2O	F
Me	Me	Amid 2	FCH_2O	F		Me	H	Amid 2	FCH_2O	F
Me	Me	Amid 3	FCH_2O	F		Me	H	Amid 3	FCH_2O	F
Me	Me	Amid 4	FCH_2O	F		Me	H	Amid 4	FCH_2O	F
Me	Me	Amid 5	FCH_2O	F		Me	H	Amid 5	FCH_2O	F
Me	Me	Amid 6	FCH_2O	F		Me	H	Amid 6	FCH_2O	F
Me	Me	Amid 7	FCH_2O	F		Me	H	Amid 7	FCH_2O	F
Me	Me	Amid 8	FCH_2O	F		Me	H	Amid 8	FCH_2O	F
Me	Me	Amid 9	FCH_2O	F		Me	H	Amid 9	FCH_2O	F
Me	Me	Amid 10	FCH_2O	F		Me	H	Amid 10	FCH_2O	F
Me	Me	Amid 11	FCH_2O	F		Me	H	Amid 11	FCH_2O	F
Me	Me	Amid 12	FCH_2O	F		Me	H	Amid 12	FCH_2O	F
Me	Me	Amid 13	FCH_2O	F		Me	H	Amid 13	FCH_2O	F
Me	Me	Amid 14	FCH_2O	F		Me	H	Amid 14	FCH_2O	F
Me	Me	Amid 15	FCH_2O	F		Me	H	Amid 15	FCH_2O	F
Me	Me	Amid 16	FCH_2O	F		Me	H	Amid 16	FCH_2O	F
Me	Me	Amid 17	FCH_2O	F		Me	H	Amid 17	FCH_2O	F
Me	Me	Amid 18	FCH_2O	F		Me	H	Amid 18	FCH_2O	F
Me	Me	Amid 19	FCH_2O	F		Me	H	Amid 19	FCH_2O	F
Me	Me	Amid 20	FCH_2O	F		Me	H	Amid 20	FCH_2O	F
Me	Me	Amid 21	FCH_2O	F		Me	H	Amid 21	FCH_2O	F
Me	Me	Amid 22	FCH_2O	F		Me	H	Amid 22	FCH_2O	F
Me	Me	Amid 23	FCH_2O	F		Me	H	Amid 23	FCH_2O	F

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 24	FCH_2O	F		Me	H	Amid 24	FCH_2O	F
Me	Me	Amid 25	FCH_2O	F		Me	H	Amid 25	FCH_2O	F
Me	Me	Amid 26	FCH_2O	F		Me	H	Amid 26	FCH_2O	F
Me	Me	Amid 27	FCH_2O	F		Me	H	Amid 27	FCH_2O	F
Me	Me	Amid 28	FCH_2O	F		Me	H	Amid 28	FCH_2O	F
Me	Me	Amid 29	FCH_2O	F		Me	H	Amid 29	FCH_2O	F
Me	Me	Amid 30	FCH_2O	F		Me	H	Amid 30	FCH_2O	F
Me	Me	Amid 1	FCH_2O	Cl		Me	H	Amid 1	FCH_2O	Cl
Me	Me	Amid 2	FCH_2O	Cl		Me	H	Amid 2	FCH_2O	Cl
Me	Me	Amid 3	FCH_2O	Cl		Me	H	Amid 3	FCH_2O	Cl
Me	Me	Amid 4	FCH_2O	Cl		Me	H	Amid 4	FCH_2O	Cl
Me	Me	Amid 5	FCH_2O	Cl		Me	H	Amid 5	FCH_2O	Cl
Me	Me	Amid 6	FCH_2O	Cl		Me	H	Amid 6	FCH_2O	Cl
Me	Me	Amid 7	FCH_2O	Cl		Me	H	Amid 7	FCH_2O	Cl
Me	Me	Amid 8	FCH_2O	Cl		Me	H	Amid 8	FCH_2O	Cl
Me	Me	Amid 9	FCH_2O	Cl		Me	H	Amid 9	FCH_2O	Cl
Me	Me	Amid 10	FCH_2O	Cl		Me	H	Amid 10	FCH_2O	Cl
Me	Me	Amid 11	FCH_2O	Cl		Me	H	Amid 11	FCH_2O	Cl
Me	Me	Amid 12	FCH_2O	Cl		Me	H	Amid 12	FCH_2O	Cl
Me	Me	Amid 13	FCH_2O	Cl		Me	H	Amid 13	FCH_2O	Cl
Me	Me	Amid 14	FCH_2O	Cl		Me	H	Amid 14	FCH_2O	Cl
Me	Me	Amid 15	FCH_2O	Cl		Me	H	Amid 15	FCH_2O	Cl
Me	Me	Amid 16	FCH_2O	Cl		Me	H	Amid 16	FCH_2O	Cl
Me	Me	Amid 17	FCH_2O	Cl		Me	H	Amid 17	FCH_2O	Cl
Me	Me	Amid 18	FCH_2O	Cl		Me	H	Amid 18	FCH_2O	Cl
Me	Me	Amid 19	FCH_2O	Cl		Me	H	Amid 19	FCH_2O	Cl
Me	Me	Amid 20	FCH_2O	Cl		Me	H	Amid 20	FCH_2O	Cl
Me	Me	Amid 21	FCH_2O	Cl		Me	H	Amid 21	FCH_2O	Cl
Me	Me	Amid 22	FCH_2O	Cl		Me	H	Amid 22	FCH_2O	Cl
Me	Me	Amid 23	FCH_2O	Cl		Me	H	Amid 23	FCH_2O	Cl
Me	Me	Amid 24	FCH_2O	Cl		Me	H	Amid 24	FCH_2O	Cl
Me	Me	Amid 25	FCH_2O	Cl		Me	H	Amid 25	FCH_2O	Cl
Me	Me	Amid 26	FCH_2O	Cl		Me	H	Amid 26	FCH_2O	Cl
Me	Me	Amid 27	FCH_2O	Cl		Me	H	Amid 27	FCH_2O	Cl
Me	Me	Amid 28	FCH_2O	Cl		Me	H	Amid 28	FCH_2O	Cl
Me	Me	Amid 29	FCH_2O	Cl		Me	H	Amid 29	FCH_2O	Cl

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 30	FCH_2O	Cl		Me	H	Amid 30	FCH_2O	Cl
Me	Me	Amid 1	FCH_2O	MeO		Me	H	Amid 1	FCH_2O	MeO
Me	Me	Amid 2	FCH_2O	MeO		Me	H	Amid 2	FCH_2O	MeO
Me	Me	Amid 3	FCH_2O	MeO		Me	H	Amid 3	FCH_2O	MeO
Me	Me	Amid 4	FCH_2O	MeO		Me	H	Amid 4	FCH_2O	MeO
Me	Me	Amid 5	FCH_2O	MeO		Me	H	Amid 5	FCH_2O	MeO
Me	Me	Amid 6	FCH_2O	MeO		Me	H	Amid 6	FCH_2O	MeO
Me	Me	Amid 7	FCH_2O	MeO		Me	H	Amid 7	FCH_2O	MeO
Me	Me	Amid 8	FCH_2O	MeO		Me	H	Amid 8	FCH_2O	MeO
Me	Me	Amid 9	FCH_2O	MeO		Me	H	Amid 9	FCH_2O	MeO
Me	Me	Amid 10	FCH_2O	MeO		Me	H	Amid 10	FCH_2O	MeO
Me	Me	Amid 11	FCH_2O	MeO		Me	H	Amid 11	FCH_2O	MeO
Me	Me	Amid 12	FCH_2O	MeO		Me	H	Amid 12	FCH_2O	MeO
Me	Me	Amid 13	FCH_2O	MeO		Me	H	Amid 13	FCH_2O	MeO
Me	Me	Amid 14	FCH_2O	MeO		Me	H	Amid 14	FCH_2O	MeO
Me	Me	Amid 15	FCH_2O	MeO		Me	H	Amid 15	FCH_2O	MeO
Me	Me	Amid 16	FCH_2O	MeO		Me	H	Amid 16	FCH_2O	MeO
Me	Me	Amid 17	FCH_2O	MeO		Me	H	Amid 17	FCH_2O	MeO
Me	Me	Amid 18	FCH_2O	MeO		Me	H	Amid 18	FCH_2O	MeO
Me	Me	Amid 19	FCH_2O	MeO		Me	H	Amid 19	FCH_2O	MeO
Me	Me	Amid 20	FCH_2O	MeO		Me	H	Amid 20	FCH_2O	MeO
Me	Me	Amid 21	FCH_2O	MeO		Me	H	Amid 21	FCH_2O	MeO
Me	Me	Amid 22	FCH_2O	MeO		Me	H	Amid 22	FCH_2O	MeO
Me	Me	Amid 23	FCH_2O	MeO		Me	H	Amid 23	FCH_2O	MeO
Me	Me	Amid 24	FCH_2O	MeO		Me	H	Amid 24	FCH_2O	MeO
Me	Me	Amid 25	FCH_2O	MeO		Me	H	Amid 25	FCH_2O	MeO
Me	Me	Amid 26	FCH_2O	MeO		Me	H	Amid 26	FCH_2O	MeO
Me	Me	Amid 27	FCH_2O	MeO		Me	H	Amid 27	FCH_2O	MeO
Me	Me	Amid 28	FCH_2O	MeO		Me	H	Amid 28	FCH_2O	MeO
Me	Me	Amid 29	FCH_2O	MeO		Me	H	Amid 29	FCH_2O	MeO
Me	Me	Amid 30	FCH_2O	MeO		Me	H	Amid 30	FCH_2O	MeO
Me	Me	Amid 1	FCH_2O	Me		Me	H	Amid 1	FCH_2O	Me
Me	Me	Amid 2	FCH_2O	Me		Me	H	Amid 2	FCH_2O	Me
Me	Me	Amid 3	FCH_2O	Me		Me	H	Amid 3	FCH_2O	Me
Me	Me	Amid 4	FCH_2O	Me		Me	H	Amid 4	FCH_2O	Me

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 5	FCH_2O	Me		Me	H	Amid 5	FCH_2O	Me
Me	Me	Amid 6	FCH_2O	Me		Me	H	Amid 6	FCH_2O	Me
Me	Me	Amid 7	FCH_2O	Me		Me	H	Amid 7	FCH_2O	Me
Me	Me	Amid 8	FCH_2O	Me		Me	H	Amid 8	FCH_2O	Me
Me	Me	Amid 9	FCH_2O	Me		Me	H	Amid 9	FCH_2O	Me
Me	Me	Amid 10	FCH_2O	Me		Me	H	Amid 10	FCH_2O	Me
Me	Me	Amid 11	FCH_2O	Me		Me	H	Amid 11	FCH_2O	Me
Me	Me	Amid 12	FCH_2O	Me		Me	H	Amid 12	FCH_2O	Me
Me	Me	Amid 13	FCH_2O	Me		Me	H	Amid 13	FCH_2O	Me
Me	Me	Amid 14	FCH_2O	Me		Me	H	Amid 14	FCH_2O	Me
Me	Me	Amid 15	FCH_2O	Me		Me	H	Amid 15	FCH_2O	Me
Me	Me	Amid 16	FCH_2O	Me		Me	H	Amid 16	FCH_2O	Me
Me	Me	Amid 17	FCH_2O	Me		Me	H	Amid 17	FCH_2O	Me
Me	Me	Amid 18	FCH_2O	Me		Me	H	Amid 18	FCH_2O	Me
Me	Me	Amid 19	FCH_2O	Me		Me	H	Amid 19	FCH_2O	Me
Me	Me	Amid 20	FCH_2O	Me		Me	H	Amid 20	FCH_2O	Me
Me	Me	Amid 21	FCH_2O	Me		Me	H	Amid 21	FCH_2O	Me
Me	Me	Amid 22	FCH_2O	Me		Me	H	Amid 22	FCH_2O	Me
Me	Me	Amid 23	FCH_2O	Me		Me	H	Amid 23	FCH_2O	Me
Me	Me	Amid 24	FCH_2O	Me		Me	H	Amid 24	FCH_2O	Me
Me	Me	Amid 25	FCH_2O	Me		Me	H	Amid 25	FCH_2O	Me
Me	Me	Amid 26	FCH_2O	Me		Me	H	Amid 26	FCH_2O	Me
Me	Me	Amid 27	FCH_2O	Me		Me	H	Amid 27	FCH_2O	Me
Me	Me	Amid 28	FCH_2O	Me		Me	H	Amid 28	FCH_2O	Me
Me	Me	Amid 29	FCH_2O	Me		Me	H	Amid 29	FCH_2O	Me
Me	Me	Amid 30	FCH_2O	Me		Me	H	Amid 30	FCH_2O	Me
Me	Me	Amid 1	FCH_2O	FCH_2O		Me	H	Amid 1	FCH_2O	FCH_2O
Me	Me	Amid 2	FCH_2O	FCH_2O		Me	H	Amid 2	FCH_2O	FCH_2O
Me	Me	Amid 3	FCH_2O	FCH_2O		Me	H	Amid 3	FCH_2O	FCH_2O
Me	Me	Amid 4	FCH_2O	FCH_2O		Me	H	Amid 4	FCH_2O	FCH_2O
Me	Me	Amid 5	FCH_2O	FCH_2O		Me	H	Amid 5	FCH_2O	FCH_2O
Me	Me	Amid 6	FCH_2O	FCH_2O		Me	H	Amid 6	FCH_2O	FCH_2O
Me	Me	Amid 7	FCH_2O	FCH_2O		Me	H	Amid 7	FCH_2O	FCH_2O
Me	Me	Amid 8	FCH_2O	FCH_2O		Me	H	Amid 8	FCH_2O	FCH_2O
Me	Me	Amid 9	FCH_2O	FCH_2O		Me	H	Amid 9	FCH_2O	FCH_2O
Me	Me	Amid 10	FCH_2O	FCH_2O		Me	H	Amid 10	FCH_2O	FCH_2O

R1	R2	R3	R6	R7		R1	R2	R3	R6	R7
Me	Me	Amid 11	FCH_2O	FCH_2O		Me	H	Amid 11	FCH_2O	FCH_2O
Me	Me	Amid 12	FCH_2O	FCH_2O		Me	H	Amid 12	FCH_2O	FCH_2O
Me	Me	Amid 13	FCH_2O	FCH_2O		Me	H	Amid 13	FCH_2O	FCH_2O
Me	Me	Amid 14	FCH_2O	FCH_2O		Me	H	Amid 14	FCH_2O	FCH_2O
Me	Me	Amid 15	FCH_2O	FCH_2O		Me	H	Amid 15	FCH_2O	FCH_2O
Me	Me	Amid 16	FCH_2O	FCH_2O		Me	H	Amid 16	FCH_2O	FCH_2O
Me	Me	Amid 17	FCH_2O	FCH_2O		Me	H	Amid 17	FCH_2O	FCH_2O
Me	Me	Amid 18	FCH_2O	FCH_2O		Me	H	Amid 18	FCH_2O	FCH_2O
Me	Me	Amid 19	FCH_2O	FCH_2O		Me	H	Amid 19	FCH_2O	FCH_2O
Me	Me	Amid 20	FCH_2O	FCH_2O		Me	H	Amid 20	FCH_2O	FCH_2O
Me	Me	Amid 21	FCH_2O	FCH_2O		Me	H	Amid 21	FCH_2O	FCH_2O
Me	Me	Amid 22	FCH_2O	FCH_2O		Me	H	Amid 22	FCH_2O	FCH_2O
Me	Me	Amid 23	FCH_2O	FCH_2O		Me	H	Amid 23	FCH_2O	FCH_2O
Me	Me	Amid 24	FCH_2O	FCH_2O		Me	H	Amid 24	FCH_2O	FCH_2O
Me	Me	Amid 25	FCH_2O	FCH_2O		Me	H	Amid 25	FCH_2O	FCH_2O
Me	Me	Amid 26	FCH_2O	FCH_2O		Me	H	Amid 26	FCH_2O	FCH_2O
Me	Me	Amid 27	FCH_2O	FCH_2O		Me	H	Amid 27	FCH_2O	FCH_2O
Me	Me	Amid 28	FCH_2O	FCH_2O		Me	H	Amid 28	FCH_2O	FCH_2O
Me	Me	Amid 29	FCH_2O	FCH_2O		Me	H	Amid 29	FCH_2O	FCH_2O
Me	Me	Amid 30	FCH_2O	FCH_2O		Me	H	Amid 30	FCH_2O	FCH_2O

Exemplary particularly preferred compounds according to the invention are those described by way of example and the salts of these compounds.

Advantageous effects

The excellent gastric protective action and the gastric acid secretion-inhibiting action of the compounds according to the invention can be demonstrated in investigations on animal experimental models. The compounds of the formula 1 according to the invention investigated in the model mentioned below have been provided with numbers, which correspond to the numbers of these compounds in the examples.

Testing of the secretion-inhibiting action on the perfused rat stomach

In Tables B-a, B-b and B-c, which follows, the influence of the compounds of the formula 1 according to aspects a, b and c of the invention on the pentagastrin-stimulated acid secretion of the perfused rat stomach after intraduodenal administration in vivo is shown.

Table B-a

No.	Dose (µmol/kg) i.d.	Inhibition of acid secretion (%)
a-3	1.0	> 50
a-8	1.0	> 50
a-12	1.0	> 50
a-13	1.0	> 50
a-20	1.0	> 50
a-33	1.0	> 50
a-34	1.0	> 50
a-35	1.0	> 50
a-36	1.0	> 50
a-37	1.0	> 50
a-38	1.0	> 50

Table B-b

No.	Dose (µmol/kg) i.d.	Inhibition of acid secretion (%)
b-2	1.0	> 50
b-5	1.0	> 50
b-6	1.0	> 50
b-7	1.0	> 50

b-9	1.0	> 50
b-10	1.0	> 50
b-11	1.0	> 50
b-12	1.0	> 50
b-13	1.0	> 50
b-17	1.0	> 50
b-18	1.0	> 50

Table B-c

No.	Dose (μmol/kg) i.d.	Inhibition of acid secretion (%)
c-3	1.0	> 50

Methodology

The abdomen of anesthetized rats (CD rat, female, 200-250 g; 1.5 g/kg i.m. urethane) was opened after tracheotomy by a median upper abdominal incision and a PVC catheter was fixed transorally in the esophagus and another via the pylorus such that the ends of the tubes just projected into the gastric lumen. The catheter leading from the pylorus led outward into the right abdominal wall through a side opening.

After thorough rinsing (about 50-100 ml), warm (37°C) physiological NaCl solution was continuously passed through the stomach (0.5 ml/min, pH 6.8-6.9; Braun-Unita I). The pH (pH meter 632, glass electrode EA 147; ϕ = 5 mm, Metrohm) and, by titration with a freshly prepared 0.01N NaOH solution to pH 7 (Dosimat 665 Metrohm), the secreted HCl were determined in the effluent in each case collected at an interval of 15 minutes.

The gastric secretion was stimulated by continuous infusion of 1 μg/kg (= 1.65 ml/h) of i.v. pentagastrin (left femoral vein) about 30 min after the end of the operation (i.e. after determination of 2 preliminary fractions). The substances to be tested were administered intraduodenally in a 2.5 ml/kg liquid volume 60 min after the start of the continuous pentagastrin infusion. The body temperature of the animals was kept at a constant 37.8-38°C by infrared irradiation and heat pads (automatic, stepless control by means of a rectal temperature sensor).

Mode(s) for Carrying Out the Invention

The examples below serve to illustrate the invention in more detail without limiting it. Further compounds of the formula 1 whose preparation is not described explicitly can likewise be prepared in an analogous manner or in a manner known per se to the person skilled in the art, using customary process techniques. The compounds named expressly as examples, and the salts of these compounds, are preferred subject matter of the invention. The abbreviation min stands for minute(s), h stands for hour(s), m.p. stands for melting point, ee for enantiomeric excess, ESI stands for electrospray ionisation, and API-ES for atmospheric pressure ionization and electrospray ionisation.

Aspect a:

a-I. Final Compounds of the formula 1 according to aspect a

a-1 Ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxylate

Ethyl 5-[2-(2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-4-hydroxy-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate (3.00 g, 6.51 mmol) was dissolved in formic acid (30 ml) and heated to 100°C for 1 h. After cooling down to room temperature, the solution was neutralized by adding a saturated aqueous solution of sodium bicarbonate and extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The crude product was crystallized using isopropyl ether to afford 2.97 g (99 %) of the title compound. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.59 (s, 1H), 7.35-7.14 (m, 4H+$CDCl_3$), 4.41 (q, 2H), 3.36 (q, 2H), 3.25-3.08 (m, 1H), 2.99-2.84 (m, 1H), 2.57 (s, 3H), 2.53-2.04 (m, 4H), 1.44 (t, 3H).

The synthesis of the following 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamides followed the procedure described above for the synthesis of ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate:

a-2 *N,N*,2,3,6'-Pentamethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above for the synthesis of ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate but starting from 4-hydroxy-*N,N*,1,2-tetramethyl-5-[2-(6-methyl-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-1*H*-benzimidazole-6-carboxamide. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.28-7.07 (m, 3H), 6.90 (s, 1H), 3.66 (s, 3H), 3.09-2.58 (m, 10H), 2.42 (s, 3H), 2.38-2.11 (m, 3H), 2.08-1.91 (m, 1H).

a-3 5'-Fluoro-*N,N*,2,3-tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above for the synthesis of ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate but starting from 5-[2-(5-

fluoro-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.44-7.31 (m, 1H), 7.24-7.02 (m, 2H), 6.91 (s, 1H), 3.66 (s, 3H), 3.13-2.58 (m, 10H), 2.42 (s, 3H), 2.39-2.14 (m, 3H), 2.11-1.92 (m, 1H).

a-4 Ethyl 5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate

The synthesis followed the procedure described above for the synthesis of ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate but starting from ethyl 5-[2-(5-fluoro-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-4-hydroxy-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.08 (s, 1H), 7.31-7.22 (m, 1H+$CDCl_3$), 6.95-6.81 (m, 2H), 4.41 (q, 2H), 3.73 (s, 3H), 3.44-3.27 (m, 2H), 3.19-3.10 (m, 1H), 2.95-2.84 (m, 1H), 2.58 (s, 3H), 2.55-2.44 (m, 1H), 2.35-2.22 (m, 2H), 2.12-2.05 (m, 1H), 1.44 (t, 3H).

a-5 6'-Fluoro-*N*,*N*,2,3-tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above for the synthesis of ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate but starting 5-[2-(6-fluoro-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.43-7.30 (m, 1H), 7.23-7.08 (m, 2H), 6.92 (s, 1H), 3.66 (s, 3H), 3.12-2.59 (m, 10H), 2.43 (s, 3H), 2.37-2.13 (m, 3H), 2.11-1.94 (m, 1H).

a-6 6'-Methoxy-*N*,*N*,2,3-tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above for the synthesis of ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate but starting from 4-hydroxy-5-[2-(6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.45 (d, 1H), 6.99-6.85 (m, 3H), 3.73, (s, 3H), 3.66 (s, 3H), 3.03 (s, 3H), 2.98-2.59 (m, 7H), 2.42 (s, 3H), 2.37-2.12 (m, 3H), 2.08-1.93 (m, 1H).

a-7 7'-Methoxy-*N*,*N*,2,3-tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above for the synthesis of ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate but starting from 4-hydroxy-5-[2-(7-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.34 (t, 1H), 6.91 (t, 2H), 6.87 (s, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.09-2.55 (m, 10H), 2.41 (s, 3H), 2.23-2.08 (m, 3H), 2.07-1.89 (m, 1H).

a-8 5'-Chloro-*N*,*N*,2,3-tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above for the synthesis of ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate but starting from 5-[2-(5-chloro-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.44 (s, 1H), 7.37 (t, 2H), 6.92 (s, 1H), 3.66 (s, 3H), 3.15-2.58 (m, 10H), 2.43 (s, 3H), 2.27-2.13 (m, 3H), 2.10-1.92 (m, 1H).

a-9 *N*,*N*,2,3,5'-Pentamethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above for the synthesis of ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate but starting from 4-hydroxy-*N*,*N*,1,2-tetramethyl-5-[2-(5-methyl-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-1*H*-benzimidazole-6-carboxamide. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.20 (d, 1H), 7.15 (s, 1H), 7.06 (d, 1H), 6.90 (s, 1H), 3.65 (s, 3H), 3.11-2.60 (m, 10H), 2.42 (s, 3H), 2.36-2.12 (m, 3H), 2.09-1.89 (m, 1H).

a-10 5'-Methoxy-*N*,*N*,2,3-tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above for the synthesis of ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate but starting from 4-hydroxy-5-[2-(5-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.23 (d, 1H), 6.96-6.73 (m, 3H), 3.77 (s, 3H), 3.66 (s, 3H), 3.12-2.60 (m, 10H), 2.42 (s, 3H), 2.39-2.10 (m, 3H), 2.08-1.87 (m, 1H).

a-11 2,3-Dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylic acid

Ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate (2.80 g, 7.43 mmol) was dissolved in dioxane (28 ml). The solution was treated with an aqueous solution of LiOH (13.2 ml; 3N) and heated to 100°C for 1 h. After cooling down to room temperature, the solution was neutralized by adding a saturated aqueous solution of ammonium chloride and after addition of solid NaCl the aqueous phase was extracted with chloroform. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was crystallized using diisopropyl ether to afford 2.21 g (85 %) of the title compound. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 12.57 (br s, 1H), 7.64 (s, 1H), 7.40-7.18 (m, 4H), 3.70 (s, 3H), 3.41-2.82 (m, 4H), 2.45 (s, 3H), 2.39-1.94 (m, 4H).

a-12 *N*,*N*,2,3-Tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

2,3-Dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylic acid (0.20 g, 0.57 mmol) was suspended in a mixture of dichloromethane (2.7 ml) and DMF (0.5 ml) and *N,N'*-carbonyldiimidazole (CDI) (0.19 g, 1.15 mmol) was added. A clear solution was formed. After one hour a solution of dimethylamine in THF (5.5 ml, 2N) was added and the reaction mixture was stirred at 60°C for 5.5 h and at room temperature for 18 h. After cooling down to room temperature, the reac-

tion mixture was poured onto water and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel using toluene:dioxane:methanol (6 : 3.8 : 0.2, v/v/v) and was crystallized using diisopropyl ether to afford 2.21 g (85 %) of the title compound as white crystals. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38-7.10 (m, 4H+$CDCl_3$), 6.78 (s, 1H), 3.67 (s, 3H), 3.23-2.08 (m, 5H), 2.98-2.86 (m, 5H), 2.61-2.46 (m, 4H), 2.42-2.30 (m, 1H), 2.29-2.19 (m, 1H), 2.13-2.03 (m, 1H).

a-13 (+)-*N,N*,2,3-Tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

Resolution of racemic *N,N*,2,3-tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide was achieved by preparative chromatography using a 250 x 30 mm CHIRALPAK® AD-H 5 µm column. The mobile phase consisted of a mixture (80 / 20, v/v) of CO_2 / (methanol + 1% diethylamine). The separation was performed at room temperature with a flow rate of 100 ml/min. The products were detected at a wavelength of 230 nm. The first-eluting enantiomer was identified as the title compound (0.50 g, 97.4 % ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38-7.10 (m, 4H+$CDCl_3$), 6.78 (s, 1H), 3.67 (s, 3H), 3.23-2.08 (m, 5H), 2.98-2.86 (m, 5H), 2.61-2.46 (m, 4H), 2.42-2.30 (m, 1H), 2.29-2.19 (m, 1H), 2.13-2.03 (m, 1H). Optical rotation: $[\alpha]^D_{20}$ = + 51° (c = 0.523 g/100 ml, methanol).

a-14 (-)-*N,N*,2,3-Tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

Resolution of racemic *N,N*,2,3-tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide was achieved by preparative chromatography using a 250 x 30 mm CHIRALPAK® AD-H 5 µm column. The mobile phase consisted of a mixture (80 / 20, v/v) of CO_2 / (methanol + 1% diethylamine). The separation was performed at room temperature with a flow rate of 100 ml/min. The products were detected at a wavelength of 230 nm. The second-eluting enantiomer was identified as the title compound (0.50 g, 99.6 % ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38-7.10 (m, 4H+$CDCl_3$), 6.78 (s, 1H), 3.67 (s, 3H), 3.23-2.08 (m, 5H), 2.98-2.86 (m, 5H), 2.61-2.46 (m, 4H), 2.42-2.30 (m, 1H), 2.29-2.19 (m, 1H), 2.13-2.03 (m, 1H). Optical rotation: $[\alpha]^D_{20}$ = - 50° (c = 0.523 g/100 ml, methanol).

a-15 2,3-Dimethyl-5-(morpholin-4-ylcarbonyl)-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,1'-indene]

2,3-Dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylic acid (0.20 g, 0.57 mmol) was suspended in a mixture of dichloromethane (3.0 ml) and DMF (0.5 ml) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumtetrafluoroborate (TBTU) (0.38 g, 1.14 mmol) was added. After 90 min, morpholine (0.19 g, 2.16 mmol) was added. A solution was formed which was stirred at room temperature for 18 h. The reaction mixture was poured onto water and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel using toluene:dioxane:methanol (6 : 3.8 : 0.2, v/v/v) and was crystallized using diisopropyl ether to afford 2.21 g

(85 %) of the title compound as white crystals. ^{1}H NMR (d_6-DMSO, 400 MHz): δ = 7.43-7.17 (m, 4H), 6.95 (s, 1H), 3.83-3.36 (m, 9H), 3.31-2.67 (m, 8H), 2.42 (s, 3H), 2.39-1.94 (m, 4H).

The synthesis of the following 2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamides followed the procedures described above either for the synthesis of *N*,*N*,2,3-tetramethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide (using CDI) or for the synthesis of 2,3-dimethyl-5-(morpholin-4-ylcarbonyl)-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene] (using TBTU):

a-16 *N*-(2-Hydroxyethyl)-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using ethanolamine and CDI as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.40-7.15 (m, 4H+$CDCl_3$), 7.01 (s, 1H), 6.67 (t, 1H), 3.80-3.52 (m, 5H), 3.50-3.30 (m, 3H), 3.24-2.62 (m, 4H), 2.51 (s, 3H), 2.44-1.88 (m, 4H).

a-17 5-[(3,3-Difluoroazetidin-1-yl)carbonyl]-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]

The synthesis followed the procedure described above using 2,2-difluoroazetidine hydrochloride and TBTU as amide coupling reagent.^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.39-7.12 (m, 4H+$CDCl_3$), 6.87 (s, 1H), 4.67-4.21 (m, 4H), 3.68 (s, 3H), 3.28-2.78 (m, 4H), 2.56 (s, 3H), 2.53-2.01 (m, 4H).

a-18 *N*-(2-Methoxyethyl)-*N*,2,3-trimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using *N*-(2-methoxyethyl)methylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.40-7.09 (m, 4H+$CDCl_3$), 6.77 (s, 1H), 3.86-3.68 (m, 5H), 3.41 (s, 3H), 3.33-2.79 (m, 10H), 2.55 (s, 3H), 2.48-1.97 (m, 4H).

a-19 2,3-Dimethyl-5-(piperidin-1-ylcarbonyl)-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]

The synthesis followed the procedure described above using piperidine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.41-7.05 (m, 4H+$CDCl_3$), 6.75 (s, 1H), 4.03-3.52 (m, 5H), 3.38-2.68 (m, 6H), 2.55 (s, 3H), 2.42-1.97 (m, 4H), 1.91-1.35 (m, 6H).

a-20 *N*-Cyclopropyl-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using cyclopropylamine and CDI as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.39-7.10 (m, 4H+$CDCl_3$), 6.91 (s, 1H), 6.05 (br s, 1H), 3.65 (s, 3H), 3.28-3.05 (m, 3H), 3.01-2.90 (m, 2H), 2.53 (s, 3H), 2.51-1.96 (m, 4H), 0.90 (q, 2H), 0.53 (q, 2H).

a-21 5-(Azetidin-1-ylcarbonyl)-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,1'-indene]

The synthesis followed the procedure described above using azetidine and CDI as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.39-7.09 (m, 4H+$CDCl_3$), 6.84 (s, 1H), 4.24 (t, 2H), 3.97 (q, 2H), 3.67 (s, 3H), 3.24-2.81 (m, 4H), 2.55 (s, 3H), 2.51-2.00 (m, 6H).

a-22 5-(Aziridin-1-ylcarbonyl)-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,1'-indene]

The synthesis followed the procedure described above using aziridine and CDI as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.64 (s, 1H), 7.34 (d, 1H), 7.30-7.22 (m, 2H+$CDCl_3$), 7.20-7.13 (m, 1H), 3.73 (s, 3H), 3.32-3.23 (m, 2H), 3.14 (dd, 1H), 2.94 (dd, 1H), 2.58 (s, 3H), 2.55-2.46 (m, 1H), 2.41 (dd, 2H), 2.33 (dd, 2H), 2.38-2.22 (m, 4H), 2.13-2.02 (m, 1H).

a-23 Methyl (3*S*)-3-{[(2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-inden]-5-yl)carbonyl]amino}-3-phenylpropanoate

The synthesis followed the procedure described above using ethyl (3*S*)-3-amino-3-phenylpropanoate and TBTU as amide coupling reagent. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 8.77 (d, 1H), 7.52-7.10 (m, 9H), 7.03 (s, 1H), 5.47 (q, 1H), 3.75-3.48 (m, 6H), 3.13-2.76 (m, 4H), 2.65 (dd, 2H), 2.43 (s, 3H), 2.32-1.86 (m, 4H).

a-24 2,3-Dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using a solution of ammonia in THF (0.5N) and TBTU as amide coupling reagent. ^{1}H NMR (d_6-DMSO, 400 MHz): δ = 7.66 (br s, 2H), 7.38-7.21 (m, 4H), 7.17 (s, 1H), 3.68 (s, 3H), 3.15-2.99 (m, 3H), 2.95-2.86 (m, 1H), 2.43 (s, 3H), 2.31-2.17 (m, 3H), 2.05-1.96 (m, 1H).

a-25 *N*-Methoxy-*N*,2,3-trimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using *N,O*-dimethylhydroxylamine hydrochloride and TBTU as amide coupling reagent. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.44-7.17 (m, 4H), 7.03 (s, 1H), 3.67 (s, 3H), 3.56 (s, 3H), 3.24 (s, 3H), 3.13-2.67 (m, 4H), 2.43 (s, 3H), 2.38- 1.94 (m, 4H).

a-26 2,3-Dimethyl-5-(pyrrolidin-1-ylcarbonyl)-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,1'-indene]

The synthesis followed the procedure described above using pyrrolidine and TBTU as amide coupling reagent. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.43-7.18 (m, 4H), 6.96 (s, 1H), 3.66 (s, 3H), 3.50 (t, 2H), 3.21-2.71 (m, 6H), 2.50 (s, 3H), 2.39-1.63 (m, 8H).

a-27 *N*,2,3-Trimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using a solution of methylamine in THF (2N) and CDI as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.38-7.11 (m, 4H+$CDCl_3$), 6.96 (s, 1H), 5.94 (d, 1H), 3.65 (s, 3H), 3.28-2.80 (m, 4H), 2.53 (s, 3H), 2.50-1.99 (m, 4H).

a-28 *N*-(2-Methoxyethyl)-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using (2-methoxy)ethylamine and CDI as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.34 (d, 1H), 7.28-7.10 (m, 3H+$CDCl_3$), 6.99 (s, 1H), 6.29 (t, 1H), 3.78-3.55 (m, 7H), 3.41 (s, 3H), 3.27-3.03 (m, 3H), 2.54 (s, 3H), 2.53-2.17 (m, 3H), 2.15-1.99 (m, 1H).

a-29 *N*-(2-Hydroxyethyl)-*N*,2,3-trimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using 2-(methylamino)ethanol and CDI as amide coupling reagent. ^{1}H NMR (d_6-DMSO, 400 MHz): δ = 12.03 (br s, 1H), 7.40-7.20 (m, 3H), 7.02 (s, 1H), 6.94-6.85 (m, 1H), 3.66 (d, 3H, rotamers), 3.51-3.40 (m, 1H), 3.38-3.12 (m, 3H), 3.09-2.65 (m, 7H), 2.42 (s, 3H), 2.39-2.25 (m, 1H), 2.23-2.15 (m, 2H), 2.08-1.95 (m, 1H).

a-30 2,3-Dimethyl-5-(4-hydroxypiperidin-1-ylcarbonyl)-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]

The synthesis followed the procedure described above using 4-hydroxypiperidine and TBTU as amide coupling reagent. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.42-7.13 (m, 4H), 6.99 (s, 1H), 4.78 (t, 1H), 4.30-3.96 (m, 1H), 3.83-3.57 (m, 4H), 3.48-2.58 (m, 7H), 2.42 (s, 3H), 2.38-2.13 (m, 3H), 2.12-1.93 (m, 1H), 1.90-1.55 (m, 2H), 1.52-1.03 (m, 2H).

a-31 (3*S*)-3-{[(2,3-Dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-inden]-5-yl)carbonyl]amino}-3-phenylpropanoic acid

Methyl (3*S*)-3-{[(2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-inden]-5-yl)carbonyl]amino}-3-phenylpropanoate (0.15 g, 0.29 mmol) was dissolved in dioxane (1.5 ml). The solution was treated with an aqueous solution of LiOH (0.53 ml; 3N) and stirred at 80°C for 3 h and room temperature for 18 h. The solution was poured onto a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude product was crystallized using diisopropyl ether to afford 0.13 g (88 %) of the title compound. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 8.94 (d, 1H), 7.55-7.16 (m, 9H), 7.10 (s, 1H), 5.40 (q, 1H), 3.68 (s, 3H), 3.18-2.62 (m, 6H), 2.43 (s, 3H), 2.35-2.09 (m, 9H), 2.05-1.86 (m, 1H).

a-32 5'-Fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylic acid

Ethyl 5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylate (11.0 g, 27.89 mmol) was dissolved in dioxane (40 ml). The solution was treated with an aqueous solution of LiOH (28.1 ml; 1.7N) and heated to 100°C for 4 h. After cooling down to room temperature, the solution was diluted with water and dichloromethane and neutralized by adding hydrochloric acid (1N). The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to form the title compounds as brown solid (6.9 g). This crude product was used as such without further purification and characterization in the following amide coupling reactions.

a-33 *N*-Ethyl-5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

5'-Fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxylic acid (crude product; 0.30 g, 0.82 mmol) was suspended in a mixture of dichloromethane (10 ml) and DMF (2.5 ml) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluroniumtetrafluoroborate (TBTU) (0.40 g, 1.23 mmol) as well as N,N-diisopropylethylamine (0.20 g, 1.22 mmol) were added. After 2 h stirring at 45°C, ethylamine hydrochloride (0.27 g, 3.27 mmol) was added. A solution was formed which was stirred at room temperature for 18 h. The reaction mixture was treated with dichloromethane and an aqueous saturated solution of sodium bicarbonate and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel using toluene:dioxane:methanol (6 : 3.8 : 0.2, v/v/v) and was crystallized using diisopropyl ether to afford 0.03 g (8 %) of the title compound as white crystals. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.26-7.18 (m, 1H+$CDCl_3$), 6.91-6.78 (m, 3H), 5.89 (t, 1H), 3.62 (s, 3H), 3.43 (quintet, 2H), 3.15-2.98 (m, 3H), 2.89-2.77 (m, 1H), 2.52-2.39 (m, 4H), 2.28-2.14 (m, 2H), 2.03-1.93 (m, 1H), 1.23 (t, 3H).

The synthesis of the following 5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamides followed the procedures described above for the synthesis of *N*-ethyl-5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide (using TBTU):

a-34 5'-Fluoro-*N*-methoxy-*N*,2,3-trimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using *N,O*-dimethylhydroxylamine hydrochloride and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30-7.22 (m, 1H+$CDCl_3$), 6.95-6.80 (m, 3H), 3.68 (s, 3H), 3.59 (br s, 3H), 3.39 (s, 3H), 3.20-3.09 (m, 1H), 3.05-2.82 (m, 3H), 2.59-2.48 (m, 4H), 2.36-2.21 (m, 2H), 2.10-2.02 (m, 1H).

a-35 *N*-Cyclopropyl-5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using cyclopropylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30-7.22 (m, 1H+$CDCl_3$), 6.97-6.82 (m, 3H), 3.68 (s, 3H), 3.21-3.08 (m, 3H), 2.99-2.82 (m, 2H), 2.58-2.47 (m, 4H), 2.33-2.21 (m, 2H), 2.10-2.00 (m, 1H), 0.96-0.87 (m, 2H), 0.70-0.61 (m, 2H).

a-36 5'-Fluoro-5-[(3-methoxyazetidin-1-yl)carbonyl]-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]

The synthesis followed the procedure described above using 3-methoxyazetidine hydrochloride and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30-7.22 (m, 1H+$CDCl_3$), 6.95-6.81 (m, 3H), 4.46-4.32 (m, 1H), 4.28-4.20 (m, 1H), 4.41-4.01 (m, 2H), 3.93-3.78 (m, 1H), 3.57 (s, 3H), 3.33 (br s, 3H), 3.20-2.82 (m, 4H), 2.59-2.45 (m, 4H), 2.37-2.21 (m, 2H), 2.11-2.00 (m, 1H).

a-37 5'-Fluoro-2,3-dimethyl-*N*-(2,2,2-trifluoroethyl)-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]-5-carboxamide

The synthesis followed the procedure described above using 2,2,2-trifluoroethylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.32-7.22 (m, 1H+$CDCl_3$), 6.99 (s, 1H), 6.97-6.82 (m, 2H), 6.26 (t, 1H), 4.22-4.08 (m, 2H), 3.67 (s, 3H), 3.20-3.03 (m, 3H), 2.98-2.82 (m, 1H), 2.59-2.44 (m, 4H), 2.35-2.21 (m, 2H), 2.10-1.98 (m, 1H).

a-38 5-(Azetidin-1-ylcarbonyl)-5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,1'-indene]

The synthesis followed the procedure described above using azetidine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.32-7.23 (m, 1H+$CDCl_3$), 6.96-6.81 (m, 3H), 4.30-4.15 (m, 2H), 4.08-3.86 (m, 2H), 3.67 (s, 3H), 3.22-2.81 (m, 4H), 2.58-2.44 (m, 4H), 2.40-2.20 (m, 4H), 2.12-2.00 (m, 2H).

a-II. Starting materials for aspect a

a-A 1-Hydroxyindane derivatives

The synthesis of methoxy-substituted 1-hydroxyindanes is described in N.M. Nguy, I.C. Chiu, H. Kohn, *J. Org. Chem.* **1987**, *52*, *9*, 1649-1655, the synthesis of methyl-substituted 1-hydroxyindanes is described in F.O. Arp, G. Fu, *J. Amer. Chem. Soc.* **2005**, *127*, *30*, 10482-10483, synthesis of halogen-substituted 1-hydroxyindanes is described in M. Olivier, E. Marechal, *Bull. Soc. Chim. Fr.* **1973**, 3092-3095 or Ulmschneider et al. *J. Med. Chem.* **2005**, *48*, *5*, 1572, respectively.

a-B Substituted (2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromides

The synthesis of 5-chloro-substituted and 5-fluoro-substituted (2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromides is described in Ulmschneider et al. *J. Med. Chem.* **2005**, *48*, *5*, 1572. The synthesis of the following substituted (2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromides follows the procedures described therein and is exemplified for the synthesis of (6-methyl-2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromide:

a-B1 (6-Methyl-2,3-dihydro-1H-inden-1-yl)triphenylphosphonium bromide

6-Methylindan-1-ol (4.8 g, 32.3 mmol) was dissolved in benzene (50 ml). Triphenylphosphonium bromide (11.1 g, 32.3 mmol) was added and the solution was stirred for 5 h under reflux and 18 h at room temperature. A white precipitate resulted. The precipitate was filtered off and washed with diethylether affording 7.89 g (52 %) of the title compound as white crystals.

^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.95-7.51 (m, 16H), 7.13-7.05 (m, 2H), 6.08 (t, 1H), 3.07-2.57 (m, 2H), 2.55-2.26 (m, 1H), 2.05 (s,3H), 1.76-1.48 (m 1H).

a-B2 (6-Fluoro-2,3-dihydro-1H-inden-1-yl)triphenylphosphonium bromide

^{1}H NMR (d_6-DMSO, 200 MHz): δ = 8.00-7.47 (m, 16H), 7.24-7.09 (m, 2H), 6.19 (t, 1H), 3.19-2.62 (m, 2H), 2.59-2.31 (m, 1H), 1.75-1.50 (m, 1H).

a-B3 (5-Methyl-2,3-dihydro-1H-inden-1-yl)triphenylphosphonium bromide:

^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.97-7.64 (m, 15H), 6.97 (s, 1H), 6.90 (d, 1H), 6.60 (dd, 1H), 6.04 (t, 1H), 3.12-2.58 (m, 2H), 2.60-2.27 (m, 1H + DMSO), 2.24 (s, 3H), 1.74-1.51 (m, 1H).

a-B4 (5-Methoxy-2,3-dihydro-1H-inden-1-yl)triphenylphosphonium bromide:

^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.93-7.70 (m, 15H), 6.74-6.59 (m, 3H), 5.95 (t, 1H), 3.69 (s, 3H), 3.03-2.83 (m, 1H), 2.76-2.62 (m, 1H), 2.49-2.34 (m, 1H + DMSO), 1.64-1.49 (m, 1H).

a-B5 (6-Methoxy-2,3-dihydro-1H-inden-1-yl)triphenylphosphonium bromide:

^{1}H NMR (d_6-DMSO, 400 MHz): δ = 8.00-7.48 (m, 15H), 7.07 (d, 1H), 6.87 (d, 1H), 6.15 (s, 1H), 5.99 (t, 1H), 3.42 (s, 3H), 3.09-2.59 (m, 2H), 2.57-2.26 (m, 1H + DMSO), 1.72-1.46 (m, 1H).

a-B6 (7-Methoxy-2,3-dihydro-1H-inden-1-yl)triphenylphosphonium bromide:

^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.90-7.60 (m, 15H), 7.26 (td, 1H), 6.71 (t, 2H), 5.95 (td, 1H), 3.10 (s, 3H), 2.97-2.61 (m, 2H), 2.55-2.26 (m, 1H + DMSO), 2.03-1.80 (m, 1H).

a-C Ethyl 4-(allyloxy)-1,2-dimethyl-1*H*-benzimidazol-6-carboxylate

To the suspension of ethyl 5-hydroxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate (21.5 g, 91.8 mmol) in acetone (260 ml) was added potassium carbonate (12.7 g, 91.8 mmmol) and allylbromide (12.0 ml, 137.6 mmmol). The reaction mixture was heated to reflux for 18 h. After cooling down to room tem-

perature, the solids were filtered off, washed with acetone, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel using toluene:dioxane:methanol (6 : 3.8 : 0.2, v/v/v) and crystallized from diisopropyl ether to afford 15.2 g (60 %) of the title compound as white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.74 (s, 1H), 7.27 (s, 1H), 6.23-6.01 (m, 1H), 5.44 (dt, 1H), 5.28 (dd, 1H), 4.85 (d, 2H), 4.34 (q, 2H), 3.76 (s, 3H), 2.54 (s, 3H), 1.35 (t, 3H).

a-D 4-(Allyloxy)-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide

To the suspension of 4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (26.7 g, 114.4 mmol) in acetonitrile (270 ml) was added potassium carbonate (17.4 g, 125.8 mmmol) and allylbromide (14.8 ml, 172.0 mmmol). The reaction mixture was heated to reflux for 3 h. After cooling down to room temperature, the reaction mixture was concentrated in vacuo. A mixture of water and dichloromethane was added to the residue, the phases were separated, and the aqueous mixture was extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using toluene:dioxane:methanol (2 : 1 : 0.5, v/v/v) to afford 16.5 g (53 %) of the title compound. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7. 03 (s, 1H), 6.72 (s, 1H), 6.25-6.06 (m, 1H), 5.48-5.24 (m, 2H), 4.83-4.80 (m, 2H), 3.70 (s, 3H), 3.07 (s, 6H), 2.60 (s, 3H).

a-E Ethyl 5-allyl-4-hydroxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate

Ethyl 4-allyloxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate (12.5 g, 45.6 mmol) was heated to 220°C for one hour. A green liquid resulted. After cooling down to room temperature, the formed solid was purified by column chromatography on silica gel using toluene:dioxane:methanol (6 : 3.5 : 0.5, v/v/v) and crystallized from diisopropyl ether to afford 10.0 g (90 %) of the title compound as white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 10.16 (br s, 1H), 7.40 (s, 1H), 6.04-5.81 (m, 1H), 4.93-4.78 (m, 2H), 4.27 (q, 2H), 3.80-3.63 (m, 5H) 2.55 (s, 3H), 1.32 (t, 3H).

a-E1 5-allyl-4-hydroxy-N,N,1,2-tetramethyl-1H-benzimidazole-6-carboxamide was prepared using the same procedure.

^{1}H NMR (d_6-DMSO, 200 MHz): δ = 10.08 (br s, 1H), 6.76 (s, 1H), 5.96-5.72 (m, 1H), 4.96-4.79 (m, 2H), 3.66 (s, 3H), 3.32 (d, 2H), 2.98 (s, 3H), 2.70 (s, 3H), 2.52 (s, 3H).

a-F Ethyl 5-allyl-4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate

To the suspension of ethyl 5-allyl-4-hydroxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate (1.00 g, 3.64 mmol) in dichloromethane (15 ml) was added at 0°C triethylamine (0.94 ml, 7.28 mmol) and pivaloyl-chloride (0.50 ml, 4.00 mmol). After stirring at room temperature for 3 h, the reaction mixture was poured onto water, the pH was adjusted to 8-9 by adding a saturated solution of sodium bicarbonate, and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue recrystallized from diisopropyl ether to afford 1.23 g (94 %) of the title compound as a white crystals. ^{1}H NMR (d_6-

DMSO, 200 MHz): δ = 7.88 (s, 1H), 5.98-5.73 (m, 1H), 5.00-4.78 (m, 2H), 4.32 (q, 2H), 3.77 (s, 3H), 3.65 (d, 2H), 2.53 (s, 3H), 1.54-1.26 (m, 12H).

a-G 5-Allyl-6-(dimethylcarbamoyl)-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalat

To the suspension of methyl ethyl 5-allyl-4-hydroxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate (16.2 g, 59.0 mmol) in dichloromethane (100 ml) was added at 0°C *N,N*-dimethylaminopyridine (0.72 g, 5.90 mmol), diethylisopropylamine (20.3 ml, 118 mmol) and pivaloylchloride (14.5 ml, 118 mmmol). After stirring at room temperature for 60 h, the reaction mixture was poured onto water, the pH was adjusted to 8-9 by adding a saturated solution of sodium bicarbonate. The phases were separated, the organic phase was washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue recrystallized from diisopropyl ether to afford 18.4 g (88 %) of the title compound as a pale brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.01 (s, 1H), 5.90-5.80 (m, 1H), 5.00-4.94 (m, 2H), 3.66 (s, 3H), 3.40 (s, 2H), 3.12 (s, 3H), 2.79 (s, 3H), 2.56 (s, 3H), 1.47 (s, 9H).

a-H Ethyl 5-(2,3-dihydroxypropyl)-4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate

To the solution of citric acid (12.3 g, 96.6 mmol) in a mixture of water (140 ml) and tert.-butanol (140 ml) ethyl 5-allyl-4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate (11.5 g, 32.0 mmol), *N*-methylmorpholine-*N*-oxide (4.12 g, 35.2 mmol), and $K_2OsO_4xH_2O$ (2.36 g, 6.41 mmol) was added. The green solution was stirred at room temperature for 4 h. The reaction mixture was neutralized by adding a saturated solution of sodium bicarbonate, diluted with water, and extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was crystallized using diisopropyl ether to afford 15 g (79 %) of the title compound as green crystals which needed no further purification. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.78 (s, 1H), 4.43 (t, 1H), 4.31 (q, 2H), 3.75 (s, 3H), 3.66-3.49 (m, 1H), 3.30 (s, 1H), 3.23 (t, 2H), 3.09-2.91 (m, 2H), 2.51-2.48 (s, 3H + DMSO), 1.39 (s, 9H), 1.35 (t, 3H).

a-I 5-(2,3-Dihydroxypropyl)-6-(dimethylcarbamoyl)-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate

To the solution of citric acid (18.6 g, 96.6 mmol) in a mixture of water (173 ml) an tert.-butanol (173 ml) 5-allyl-6-(dimethylcarbamoyl)-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalat (17.3 g, 48.3 mmol), *N*-methylmorpholine-*N*-oxide (6.22 g, 53.1 mmol), and $K_2OsO_4xH_2O$ (3.55 g, 9.70 mmol) was added. The solution was stirred at room temperature for 18 h. The pH-value was adjusted to 8-9 by adding a saturated solution of sodium bicarbonate. The aqueous mixture was concentrated to one half and, after addition of solid sodium chloride, extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was recrystallized from isopropanol to afford 15 g (79 %) of the title compound as a white solid. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.28 (s, 1H), 4.46 (t, 1H), 3.71 (s, 3H), 3.60 (m, 1H), 3.30 (s, 1H), 3.22 (t, 2H), 3.03 (s, 3H), 2.82 (s, 3H), 2.58-2.36 (m, 5H + DMSO), 1.38 (s, 9H).

a-J Ethyl 4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazole-6-carboxylate

The solution of ethyl 5-(2,3-dihydroxypropyl)-4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate (12.0 g, 30.57 mmol) in methanol (270 ml) was cooled to 0°C and a solution of $NaIO_4$ (13.1 g, 61.15 mmol) in water (110 ml) was added during a period of 30 min. The solution was stirred for 3 h in which a white precipitate was formed. The reaction mixture was poured onto water (500 ml). The aqueous phase was extracted with dichloromethane, the combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was crystallized using diisopropyl ether to afford 9.83 g (89 %) of the title compound as white crystals which needed no further purification. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 9.60 (s, 1H), 8.04 (s, 1H), 4.30 (q, 2H), 3.95 (s, 2H), 3.80 (s, 3H), 2.55 (s, 3H), 1.36 (s, 9H), 1.33 (t, 3H).

a-K 6-(Dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate

The suspension of 5-(2,3-dihydroxypropyl)-6-(dimethylcarbamoyl)-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate (28.4 g, 72.54 mmol) in methanol (650 ml) was cooled to 0°C and a solution of $NaIO_4$ (31.0 g, 145.0 mmol) was added during a period of 45 min. The solution was stirred for 2 h in which a white precipitate was formed. Water was added until a solution resulted. The aqueous phase was extracted with dichloromethane, the combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was crystallized using diisopropyl ether to afford 24.32 g (93 %) of the title compound as pale brown crystals which needed no further purification. The ^{1}H-NMR spectrum shows a mixture of the aldehyde and the corresponding enol in a ration 2:3: ^{1}H NMR (d_6-DMSO, 200 MHz): aldehyde-form: δ = 9.50 (s, 1H), 7.41 (s, 1H), 3.74 (s, 3H), 3.55 (d, 2H), 3.01 (s, 3H), 2.82 (s, 3H), 2.54-2.38 (m, 3H + DMSO), 1.35 (s, 9H); enol-form: δ = 7.29 (s, 1H), 6.21 (br s, 1H), 4.51 (q, 1H), 3.71 (s, 3H), 3.13 (s, 1H), 3.03 (s, 3H), 2.83 (s, 3H), 2.54-2.38 (m, 3H + DMSO), 1.38 (s, 9H).

a-L Ethyl 5-[2-(2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate

(2,3-Dihydro-1*H*-inden-1-yl)triphenylphosphonium bromide (14.28 g, 31.00 mmol) and K_2CO_3 (10.72 g, 77.6 mmol) were added to the degassed solution of 18-crown-6 (0.42 g) in dichloroethane (90 ml). The suspension was heated to 80°C and ethyl 4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazole-6-carboxylate (2.80 g, 7.76 mmol) was added. The reaction mixture was stirred for 45 min at this temperature and, after cooling down to room temperature, treated with a saturated solution of ammonium chloride. The aqueous phase was extracted with dichloromethane, the combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified using flash column chromatography on silica gel using toluene:dioxane:methanol (6 : 3.9 : 0.1, v/v/v) and crystallized using a mixture of isopropyl ether and petrol ether to afford 0.77 g (22 %) of the title compound as slightly green crystals. The ^{1}H-NMR spectrum shows a mixture of the two stereoisomers concerning the double bond: ^{1}H NMR (d_6-DMSO, 200 MHz):

δ = 7.88 + 7.85 (s, 1H), 7.35-7.05 (m, 4H+$CDCl_3$), 5.81 + 5.30 (quint, 1H), 4.30 + 4.21 (q, 2H), 4.08-3.67 (m, 5H), 3.00-2.37 (m, 7H + DMSO), 1.42-1.08 (m, 12 H).

The following compounds were synthesized using the same procedure:

a-L1 Ethyl 4-[(2,2-dimethylpropanoyl)oxy]-5-[2-(5-fluoro-2,3-dihydro-1H-inden-1-ylidene)ethyl]-1,2-dimethyl-1H-benzimidazole-6-carboxylate

The synthesis followed the procedure described above using ethyl 4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazole-6-carboxylate and (5-fluoro-2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromide as starting materials. MS (ESI) = 479.1 (MH^+).

a-L2 6-(Dimethylcarbamoyl)-5-[2-(5-fluoro-2,3-dihydro-1H-inden-1-ylidene)ethyl]-1,2-dimethyl-1H-benzimidazol-4-yl pivalate

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate and (5-fluoro-2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromide as starting materials. MS (API-ES) = 478.2 (MH^+).

a-L3 6-(dimethylcarbamoyl)-5-[2-(6-fluoro-2,3-dihydro-1H-inden-1-ylidene)ethyl]-1,2-dimethyl-1H-benzimidazol-4-yl pivalate

The synthesis followed the procedure described above but 6-(dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate and (6-fluoro-2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromide as starting materials. MS (API-ES) = 478.2 (MH^+).

a-L4 6-(dimethylcarbamoyl)-5-[2-(5-methoxy-2,3-dihydro-1H-inden-1-ylidene)ethyl]-1,2-dimethyl-1H-benzimidazol-4-yl pivalate

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate and (5-methoxy-2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromide as starting materials. MS (API-ES) = 490.2 (MH^+).

a-L5 6-(dimethylcarbamoyl)-5-[2-(6-methoxy-2,3-dihydro-1H-inden-1-ylidene)ethyl]-1,2-dimethyl-1H-benzimidazol-4-yl pivalate

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate and (6-methoxy-2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromide as starting materials. MS (API-ES) = 490.2 (MH^+).

a-L6 6-(dimethylcarbamoyl)-5-[2-(7-methoxy-2,3-dihydro-1H-inden-1-ylidene)ethyl]-1,2-dimethyl-1H-benzimidazol-4-yl pivalate

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate and (7-methoxy-2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromide as starting materials. MS (API-ES) = 490.2 (MH^+).

a-L7 5-[2-(5-chloro-2,3-dihydro-1H-inden-1-ylidene)ethyl]-6-(dimethylcarbamoyl)-1,2-dimethyl-1H-benzimidazol-4-yl pivalate

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate and (5-chloro-2,3-dihydro-1*H*-inden-1- yl)triphenylphosphonium bromide as starting materials. The compound was used in the next step without further characterization.

a-L8 6-(dimethylcarbamoyl)-1,2-dimethyl-5-[2-(5-methyl-2,3-dihydro-1H-inden-1-ylidene)ethyl]-1H-benzimidazol-4-yl pivalate

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate and (5-methyl-2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromide as starting materials. MS (ESI) = 474.1 (MH^+).

a-L9 6-(dimethylcarbamoyl)-1,2-dimethyl-5-[2-(6-methyl-2,3-dihydro-1H-inden-1-ylidene)ethyl]-1H-benzimidazol-4-yl pivalate

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate and (6-methyl-2,3-dihydro-1*H*-inden-1-yl)triphenylphosphonium bromide as starting materials. The compound was used in the next step without further characterization.

a-M Ethyl-5-[2-(2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-4-hydroxy-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate

The solution of ethyl 5-[2-(2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate (0.45 g, 0.98 mmol) in dioxane (4.5 ml) was heated to 100°C and treated with an aqueous solution of $LiOHxH_2O$ (1 ml, 3N). The reaction mixture was stirred for 90 min at this temperature in which a white precipitate resulted. After cooling down to room temperature, a saturated solution of ammonium chloride was added, the aqueous phase was extracted with dichloromethane, the combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was crystallized using isopropyl ether to afford 0.34 g (93 %) of the title compound.

The ^{1}H-NMR spectrum shows a mixture of the two stereoisomers concerning the double bond:

^{1}H NMR (d_6-DMSO, 200 MHz): δ = 8.77 (br s, 1H), 7.38 (s, 1H), 7.35-7.03 (m, 4H), 5.94 + 5.40 (quint, 1H), 4.38-4.05 + 3.84 (m + d, 4H), 3.71 (s, 3H), 3.05-2.69 (m, 4H), 2.55 (s, 3H), 1.30 + 1.18 (t, 3H).

The following compounds were synthesized using the same procedure:

a-M1 Ethyl 5-[2-(5-fluoro-2,3-dihydro-1H-inden-1-ylidene)ethyl]-4-hydroxy-1,2-dimethyl-1H-benzimidazole-6-carboxylate

The synthesis followed the procedure described above but using ethyl 4-[(2,2-dimethylpropanoyl)oxy]-5-[2-(5-fluoro-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate as starting material. MS (ESI) = 395.0 (MH^+).

a-M2 5-[2-(5-Fluoro-2,3-dihydro-1H-inden-1-ylidene)ethyl]-4-hydroxy-N,N,1,2-tetramethyl-1H-benzimidazole-6-carboxamide

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-5-[2-(5-fluoro-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate as starting material. MS (API-ES) = 394.2 (MH^+).

a-M3 5-[2-(6-Fluoro-2,3-dihydro-1H-inden-1-ylidene)ethyl]-4-hydroxy-N,N,1,2-tetramethyl-1H-benzimidazole-6-carboxamide

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-5-[2-(6-fluoro-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate as starting material. MS (API-ES) = 394.2 (MH^+).

a-M4 4-Hydroxy-5-[2-(5-methoxy-2,3-dihydro-1H-inden-1-ylidene)ethyl]-N,N,1,2-tetramethyl-1H-benzimidazole-6-carboxamide

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-5-[2-(5-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate as starting material. MS (API-ES) = 406.1 (MH^+).

a-M5 4-Hydroxy-5-[2-(6-methoxy-2,3-dihydro-1H-inden-1-ylidene)ethyl]-N,N,1,2-tetramethyl-1H-benzimidazole-6-carboxamide

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-5-[2-(6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate as starting material. MS (API-ES) = 406.2 (MH^+).

a-M6 4-Hydroxy-5-[2-(7-methoxy-2,3-dihydro-1H-inden-1-ylidene)ethyl]-N,N,1,2-tetramethyl-1H-benzimidazole-6-carboxamide

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-5-[2-(7-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate as starting material. MS (API-ES) = 406.2 (MH^+).

a-M7 5-[2-(5-Chloro-2,3-dihydro-1H-inden-1-ylidene)ethyl]-4-hydroxy-N,N,1,2-tetramethyl-1H-benzimidazole-6-carboxamide

The synthesis followed the procedure described above but using 5-[2-(5-chloro-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-6-(dimethylcarbamoyl)-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate as starting material. MS (API-ES) = 410.1, 412.1 (MH^+).

a-M8 4-Hydroxy-N,N,1,2-tetramethyl-5-[2-(5-methyl-2,3-dihydro-1H-inden-1-ylidene)ethyl]-1H-benzimidazole-6-carboxamide

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-1,2-dimethyl-5-[2-(5-methyl-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-1*H*-benzimidazol-4-yl pivalate as starting material. The ^{1}H-NMR spectrum shows a mixture of the two stereoisomers concerning the double bond: ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 10.12 (br s, 1H), 7.64 + 7.57 (s, 1H), 7.27-6.88 (m, 2H), 6.76 + 6.74 (s, 1H), 5.83 + 5.43 (t, 1H), 3.66 (s, 3H), 3.47 (d, 1H), 3.15-2.58 (m, 11H), 2.31 + 2.25 (s, 3H).

a-M 9 4-Hydroxy-N,N,1,2-tetramethyl-5-[2-(6-methyl-2,3-dihydro-1H-inden-1-ylidene)ethyl]-1H-benzimidazole-6-carboxamide

The synthesis followed the procedure described above but using 6-(dimethylcarbamoyl)-1,2-dimethyl-5-[2-(6-methyl-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]-1*H*-benzimidazol-4-yl pivalate as starting material. The ^{1}H-NMR spectrum shows a mixture of the two stereoisomers concerning the double bond: ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 10.12 (br s, 1H), 7.72-7.46 (m, 1H), 7.25-6.87 (m, 2H), 6.76 + 6.74 (s, 1H), 5.89 + 5.48 (t, 1H), 3.66 (s, 3H), 3.46 (d, 1H), 3.13-2.58 (m, 11H), 2.53 (s, 3H), 2.34 + 2.23 (s, 3H).

Aspect b:

b-I. Final Compounds of the formula 1 according to aspect b

b-1 Ethyl 2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxylate

methodology 1:

The solution of ethyl 2,3-dimethyl-1',3'-dihydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxylate (75 mg, 0.200 mmol) in ethanol (40 ml) was treated with palladium on charcoal (10%) and hydrogenated under an atmosphere of hydrogen for 2.5 h. The catalyst was filtered off and the filtrate was concentrated in vacuo. The resulting oil was crystallized with diisopropyl ether to afford 56 mg (75 %) of the title compound.

methodology 2:

i.) alkene cross-metathesis: A solution of 2-methyleneindane (4.17 g, 32.0 mmol) in dichloroethane (10 ml) was added to a solution of 5-allyl-4-{[dimethyl(1,1,2-trimethylpropyl)silyl]oxy}-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (2.67 g, 6.40 mmol) in dry dichloroethane (100 ml). After stirring for 10 min at room temperature, second generation Grubbs catalyst (815 mg, 0.96 mmol) was added and the brown suspension was stirred for 2 h at 80°C. Further 2-methyleneindane (0.20 g, 1.50 mmol) and further second generation Grubbs catalyst (20 mg, 0.02 mmol) were added and stirring at 80°C was continued for 30 min. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel using dichloromethane:triethylamine (100 : 0.25, v/v) afforded 2.37 g of a dark oil which was used immediately in the next step.

ii.) deprotection: The solution of the crude product of the alkene cross-metathesis step before (2.37 g, ≈ 4.56 mmol) in THF (25 ml) was cooled to 0°C and treated with a solution of tetrabutylammonium fluoride in THF (5.50 ml, 5.48 mmol, 1M). After stirring at 0°C for 1.5 h, the reaction mixture was poured onto water and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using toluene:dioxane:methanol (7 : 3.5 : 0.5, v/v/v) affording 0.43 g of a brown solid which was used immediately in the next step.

iii.) cyclization: The solution of the crude product of the deprotection step before (0.43 g, ≈ 1.14 mmol) in acetic acid (40 ml) was cooled to 15°C and treated carefully with sulfuric acid (20 ml). After stirring at 50°C for 1.5 h, the reaction mixture was poured onto ice water, the aqueous phase was neutralized with 6N NaOH and extracted with ethyl acetate. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified first by column chromatography on silica gel using toluene:dioxane:methanol (7 : 3 : 0.25, v/v/v) and, finally, by preparative HPLC using a 125 x 20 mm GROM Saphir 65 C8 5 µm column (mobile phase: A – ammonium formate puffer pH 3.75, B – acetonitrile; flow rate: 30 ml/min) to afford 0.07 g (9 %) of the title compound as white crystals. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.58 (s, 1H), 7.19-7.11 (m, 4H), 4.40 (q, 2H), 3.72 (s, 3H), 3.44 (d, 2H), 3.30 (t, 2H), 3.17 (d, 2H), 2.57 (s, 3H), 2.13 (t, 2H), 1.44 (t, 3H).

b-2 *N*,*N*,2,3-tetramethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxamide

The suspension of 4-hydroxy-5-[2-(1*H*-inden-2-yl)ethyl]-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (1.27 g, 3.38 mmol) in orthophosphoric acid (10 ml) was heated for 15 min at a temperature of 80°C (oil-bath). The mixture was poured onto ice water, the aqueous phase was neutralized with 10 N NaOH and extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified first by column chromatography on silica gel using toluene:dioxane:methanol:ammonia (20 : 10 : 2 : 0.5, v/v/v/v) and, finally, by preparative HPLC using a 75 x 30 mm Penomenex Gemini AXIA C18 5 µm column (mobile phase: A – ammonium formate puffer pH 3.75, B – acetonitrile; flow rate: 40 ml/min) to afford 0.05 g (4 %) of the title compound as white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.16 (s, 4H), 6.75 (s, 1H), 3.65 (s, 3H), 3.46 (d, 2H), 3.13 (s, 3H), 3.16 (d, 2H), 3.03-2.79 (m, 5H), 2.54 (s, 3H), 2.13 (t, 2H).

b-3 2,3-Dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxylic acid

Ethyl 2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxylate (60 mg, 0.16 mmol) was dissolved in a mixture of dioxane (2 ml) and water (0.5 ml). The solution was treated with an aqueous solution of LiOH (80 µl; 6N) and heated to 100°C for 2 h. After cooling down to room temperature, the reaction mixture was neutralized by adding 2N HCl, concentrated in vacuo and dried at 40°C in vacuo over night. The crude product (100 mg) was used as such without further purification and characterization in the following amidation steps.

b-4 *N*,2,3-Trimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxamide

2,3-Dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxylic acid (crude product; 85 mg, 0.137 mmol) was suspended in a mixture of dichloromethane (5 ml) and DMF (1 ml) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluroniumtetrafluoroborate (TBTU) (66 mg, 0.206 mmol) was added. A clear solution was formed. After 1.5 h, a solution of methylamine in THF (0.30 ml, 0.60 mmol, 2N) was added and the reaction mixture was stirred at 60°C for 1.5 h. After cooling down to room temperature, the reaction mixture was poured onto water and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel using toluene:dioxane:methanol (6 : 3.5 : 0.5, v/v/v) and was crystallized using diisopropyl ether and dichloromethane to afford 25 mg (43 %) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.20-7.11 (m, 4H), 6.94 (s, 1H), 5.92 (s, 1H), 3.65 (s, 3H), 3.45 (d, 2H), 3.16 (d, 2H), 3.09 (t, 2H), 3.03 (d, 3H), 2.54 (s, 3H), 2.10 (t, 2H).

b-5 *N*-cyclopropyl-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using cyclopropylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.15 (s, 4H), 6.94 (s, 1H), 6.09 (s, 1H), 3.67 (s, 3H), 3.42 (d, 2H), 3.14 (d, 2H), 3.09 (t, 2H), 2.97-2.88 (m, 1H), 2.52 (s, 3H), 2.10 (t, 2H), 0.94-0.86 (m, 2H), 0.69-0.61 (m, 2H).

b-6 5-(Azetidin-1-ylcarbonyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,2'-indene]

The synthesis followed the procedure described above using azetidine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.16 (s, 4H), 6.81 (s, 1H), 4.24 (t, 2H), 3.96 (t, 2H), 3.66 (s, 3H), 3.45 (d, 2H), 3.14 (d, 2H), 3.01 (t, 2H), 2.54 (s, 3H), 2.32 (quint, 2H), 2.13 (t, 2H).

b-7 *N*-methoxy-*N*,2,3-trimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using *N,O*-dimethylhydroxylamine hydrochloride and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.16 (s, 4H), 6.86 (s, 1H), 3.67 (s, 3H), 3.59 (s, 3H), 3.45 (d, 2H), 3.33 (s, 3H), 3.14 (d, 2H), 2.94 (t, 2H), 2.55 (s, 3H), 2.13 (t, 2H).

b-8 *N*-isobutyl-*N*,2,3-trimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using *N*-methylisobutylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.16 (s, 4H), 6.73 (s, 1H), 3.65 (s, 3H), 3.53-3.36 (m, 3H), 3.21-2.80 (m, 7H), 2.55 (s, 3H), 2.14 (t, 2H), 1.03 (d, 3H), 0.80 (d, 3H).

b-9 *N*-cyclobutyl-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using cyclobutylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.15 (s, 4H), 6.93 (s, 1H), 6.07 (d, 1H), 4.61 (dd, 1H), 3.66 (s, 3H), 3.45 (d, 2H), 3.14 (d, 2H), 3.08 (t, 2H), 2.59-2.38 (m, 5H), 2.09 (t, 2H), 2.03-1.70 (m, 4H).

b-10 *N*-(cyclopropylmethyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using cyclopropanemethylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.15 (s, 4H), 6.96 (s, 1H), 6.07 (t, 1H), 3.66 (s, 3H), 3.53-3.29 (m, 4H), 3.20-3.05 (m, 4H), 2.10 (t, 2H), 1.26-1.00 (m, 1H), 0.63-0.52 (m, 2H), 0.36-0.25 (m, 2H).

b-11 *N*-ethyl-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using a solution of ethylamine in THF (2M) and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.15 (s, 4H), 6.95 (s, 1H), 5.91 (t, 1H), 3.66 (s, 3H), 3.53 (q, 2H), 3.43 (d, 2H), 3.14 (d, 2H), 3.09 (t, 2H), 2.53 (s, 3H), 2.10 (t, 2H), 1.29 (t, 3H).

b-12 5-[(3-Methoxyazetidin-1-yl)carbonyl]-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]

The synthesis followed the procedure described above using 3-methoxyazetidine hydrochloride and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.20-7.10 (m, 4H), 6.82 (s, 1H), 4.44-4.30 (m, 1H), 4.29-4.19 (m, 1H), 4.13-4.01 (m, 2H), 3.90-3.79 (m, 1H), 3.66 (s, 3H), 3.43 (d, 2H), 3.32 (s, 3H), 3.14 (d, 2H), 3.06-2.92 (m, 2H), 2.54 (s, 3H), 2.13 (t, 2H).

b-13 5-(Isoxazolidin-2-ylcarbonyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,2'-indene]

The synthesis followed the procedure described above using isoxazolidine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.20-7.13 (m, 4H), 6.94 (s, 1H), 4.00 (t, 2H), 3.85 (t, 2H), 3.67 (s, 3H), 3.44 (d, 2H), 3.14 (d, 2H), 3.01 (t, 2H), 2.54 (s, 3H), 2.38 (quintet, 2H), 2.12 (t, 2H).

b-14 2,3-Dimethyl-5-(1,2-oxazinan-2-ylcarbonyl)-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]

The synthesis followed the procedure described above using 1,2-oxazinane and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.20-7.13 (m, 4H), 6.87 (s, 1H), 4.03-3.74 (m, 4H), 3.67 (s, 3H), 3.42 (d, 2H), 3.13 (d, 2H), 2.98 (t, 2H), 2.54 (s, 3H), 2.13 (t, 2H), 1.94-1.75 (m, 4H).

b-15 *N*-(2-Hydroxyethyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using ethanolamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.15 (s, 4H), 6.91 (s, 1H), 6.53 (t, 1H), 3.83 (t, 2H), 3.66-3.58 (m, 5H), 3.39 (d, 2H), 3.12 (d, 2H), 2.99 (t, 2H), 2.50 (s, 3H), 2.04 (t, 2H), 2.00 (s, 1H).

b-16 2,3-Dimethyl-*N*-(2,2,2-trifluoroethyl)-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using 2,2,2-trifluoroethylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.19-7.14 (m, 4H), 6.97 (s, 1H), 6.26 (t, 1H), 4.14-4.08 (m, 2H), 3.51 (s, 3H), 3.45 (d, 2H), 3.16 (d, 2H), 3.08 (t, 2H), 2.54 (s, 3H), 2.11 (t, 2H).

b-17 2,3-Dimethyl-5-(pyrrolidin-1-ylcarbonyl)-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,2'-indene]

The synthesis followed the procedure described above using pyrrolidine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.19-7.13 (m, 4H), 6.78 (s, 1H), 3.69 (t, 2H), 3.65 (s, 3H), 3.44 (d, 2H), 3.18 (t, 2H), 3.13 (d, 2H), 2.88 (t, 2H), 2.54 (s, 3H), 2.13 (t, 2H), 2.04-1.86 (m, 4H).

b-18 *N*-(2-Ethoxyethyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using 2-ethoxyethylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.20-7.13 (m, 4H), 6.98 (s, 1H), 6.28 (t, 1H), 3.74-3.60 (m, 4H), 3.56 (q, 2H), 3.45 (d, 2H), 3.15 (d, 2H), 3.10 (t, 2H), 2.55 (s, 3H), 2.11 (t, 2H), 1.23 (t, 3H).

b-19 *N*-(3-Methoxypropyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using 3-methoxypropylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.19-7.12 (m, 4H), 6.97 (s, 1H), 6.47 (t, 1H), 3.66 (s, 3H), 3.62-3.53 (m, 4H), 3.44 (d, 2H), 3.36 (s, 3H), 3.10 (t, 2H), 2.54 (s, 3H), 2.11 (t, 2H), 1.92 (quintet, 2H).

b-20 2,3-Dimethyl-*N*-[2-(methylthio)ethyl]-1',3',6,7-tetrahydro-*3H*-spiro[chromeno[7,8-*d*]-imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using 2-(methylthio)ethylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.19-7.12 (m, 4H), 6.98 (s, 1H), 6.34 (t, 1H), 3.72-3.61 (m, 5H), 3.43 (d, 2H), 3.69-3.08 (m, 4H), 2.80 (t, 2H), 2.53 (s, 3H), 2.17 (s, 3H), 2.11 (t, 2H).

b-21 *N*-(2-Methoxyethyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3*H*-spiro[chromeno[7,8-*d*]-imidazole-8,2'-indene]-5-carboxamide

The synthesis followed the procedure described above using 2-methoxyethylamine and TBTU as amide coupling reagent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.19-7.13 (m, 4H), 6.97 (s, 1H), 6.27 (t, 1H), 3.73-3.58 (m, 7H), 3.44 (d, 2H), 3.41 (s, 3H), 3.15 (d, 2H), 3.10 (t, 2H), 2.54 (s, 3H), 2.11 (t, 2H).

b-II. Starting materials for aspect b

b-A Ethyl 4-(allyloxy)-1,2-dimethyl-1*H*-benzimidazol-6-carboxylate

To the suspension of ethyl 5-hydroxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate (21.5 g, 91.8 mmol) in acetone (260 ml) was added potassium carbonate (12.7 g, 91.8 mmmol) and allylbromide (12.0 ml, 137.6 mmmol). The reaction mixture was heated to reflux for 18 h. After cooling down to room temperature, the solids were filtered off, washed with acetone, and the filtrate was concentrated in vacuo.

The residue was purified by column chromatography on silica gel using toluene:dioxane:methanol (6 : 3.8 : 0.2, v/v/v) and crystallized from diisopropyl ether to afford 15.2 g (60 %) of the title compound as white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.74 (s, 1H), 7.27 (s, 1H), 6.23-6.01 (m, 1H), 5.44 (dt, 1H), 5.28 (dd, 1H), 4.85 (d, 2H), 4.34 (q, 2H), 3.76 (s, 3H), 2.54 (s, 3H), 1.35 (t, 3H).

b-B 4-(Allyloxy)-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide

To the suspension of 4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (26.7 g, 114.4 mmol) in acetonitrile (270 ml) was added potassium carbonate (17.4 g, 125.8 mmmol) and allylbromide (14.8 ml, 172.0 mmmol). The reaction mixture was heated to reflux for 3 h. After cooling down to room temperature, the reaction mixture was concentrated in vacuo. A mixture of water and dichloromethane was added to the residue, the phases were separated, and the aqueous mixture was extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using toluene:dioxane:methanol (2 : 1 : 0.5, v/v/v) to afford 16.5 g (53 %) of the title compound. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7. 03 (s, 1H), 6.72 (s, 1H), 6.25-6.06 (m, 1H), 5.48-5.24 (m, 2H), 4.83-4.80 (m, 2H), 3.70 (s, 3H), 3.07 (s, 6H), 2.60 (s, 3H).

b-C Ethyl 5-allyl-4-hydroxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate

Ethyl 4-allyloxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate (12.5 g, 45.6 mmol) was heated to 220°C for one hour. A green liquid resulted. After cooling down to room temperature, the formed solid was purified by column chromatography on silica gel using toluene:dioxane:methanol (6 : 3.5 : 0.5, v/v/v) and crystallized from diisopropyl ether to afford 10.0 g (90 %) of the title compound as white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 10.16 (br s, 1H), 7.40 (s, 1H), 6.04-5.81 (m, 1H), 4.93-4.78 (m, 2H), 4.27 (q, 2H), 3.80-3.63 (m, 5H) 2.55 (s, 3H), 1.32 (t, 3H).

b-C1 5-allyl-4-hydroxy-N,N,1,2-tetramethyl-1H-benzimidazole-6-carboxamide was prepared using the same procedure.

^{1}H NMR (d_6-DMSO, 200 MHz): δ = 10.08 (br s, 1H), 6.76 (s, 1H), 5.96-5.72 (m, 1H), 4.96-4.79 (m, 2H), 3.66 (s, 3H), 3.32 (d, 2H), 2.98 (s, 3H), 2.70 (s, 3H), 2.52 (s, 3H).

b-D Ethyl 5-allyl-4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate

To the suspension of ethyl 5-allyl-4-hydroxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate (1.00 g, 3.64 mmol) in dichloromethane (15 ml) was added at 0°C triethylamine (0.94 ml, 7.28 mmol) and pivaloyl-chloride (0.50 ml, 4.00 mmol). After stirring at room temperature for 3 h, the reaction mixture was poured onto water, the pH was adjusted to 8-9 by adding a saturated solution of sodium bicarbonate, and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue recrystallized from diisopropyl ether to afford 1.23 g (94 %) of the title compound as a white crystals. ^{1}H NMR (d_6-

DMSO, 200 MHz): δ = 7.88 (s, 1H), 5.98-5.73 (m, 1H), 5.00-4.78 (m, 2H), 4.32 (q, 2H), 3.77 (s, 3H), 3.65 (d, 2H), 2.53 (s, 3H), 1.54-1.26 (m, 12H).

b-E 5-Allyl-6-(dimethylcarbamoyl)-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalat

To the suspension of methyl ethyl 5-allyl-4-hydroxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate (16.2 g, 59.0 mmol) in dichloromethane (100 ml) was added at 0°C *N,N*-dimethylaminopyridine (0.72 g, 5.90 mmol), diethylisopropylamine (20.3 ml, 118 mmol) and pivaloylchloride (14.5 ml, 118 mmmol). After stirring at room temperature for 60 h, the reaction mixture was poured onto water, the pH was adjusted to 8-9 by adding a saturated solution of sodium bicarbonate. The phases were separated, the organic phase was washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue recrystallized from diisopropyl ether to afford 18.4 g (88 %) of the title compound as a pale brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.01 (s, 1H), 5.90-5.80 (m, 1H), 5.00-4.94 (m, 2H), 3.66 (s, 3H), 3.40 (s, 2H), 3.12 (s, 3H), 2.79 (s, 3H), 2.56 (s, 3H), 1.47 (s, 9H).

b-F 5-allyl-4-{[dimethyl(1,1,2-trimethylpropyl)silyl]oxy}-*N,N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide

To the suspension of ethyl 5-allyl-4-hydroxy-2,3-dimethyl-1*H*-benzimidazol-6-carboxylate (4.94 g, 18.0 mmol) in DMF (60 ml) was added imidazole (2.48 g, 36.0 mmol) and a solution of thexyldimethylchlorosilane (4.5 ml, 21.6 mmol) in DMF (5 ml). After stirring at 90°C for 4.5 h and at room temperature for 18 h, the reaction mixture was poured onto ice water, the pH was adjusted to 8-9 by adding a saturated solution of sodium bicarbonate, and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water and a saturated solution of sodium bicarbonate, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue recrystallized from ethanol to afford 5.69 g (76 %) of the title compound as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.43 (s, 1H), 6.07-5.87 (m, 1H), 4.95-4.73 (m, 2H), 4.35 (q, 2H), 3.98-3.87 (m, 2H), 3.68 (s, 3H), 2.55 (s, 3H), 1.88 (quint, 1H), 1.39 (t, 3H), 1.04 (s, 6H), 0.97 (d, 6H), 0.36 (s, 6H).

b-G Ethyl 5-(2,3-dihydroxypropyl)-4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate

To the solution of citric acid (12.3 g, 96.6 mmol) in a mixture of water (140 ml) and tert.-butanol (140 ml) ethyl 5-allyl-4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate (11.5 g, 32.0 mmol), *N*-methylmorpholine-*N*-oxide (4.12 g, 35.2 mmol), and $K_2OsO_4xH_2O$ (2.36 g, 6.41 mmol) was added. The green solution was stirred at room temperature for 4 h. The reaction mixture was neutralized by adding a saturated solution of sodium bicarbonate, diluted with water, and extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was crystallized using diisopropyl ether to afford 15 g (79 %) of the title compound as green crystals which needed no further purification. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.78 (s, 1H), 4.43 (t, 1H), 4.31 (q, 2H), 3.75 (s, 3H), 3.66-3.49 (m, 1H), 3.30 (s, 1H), 3.23 (t, 2H), 3.09-2.91 (m, 2H), 2.51-2.48 (s, 3H + DMSO), 1.39 (s, 9H), 1.35 (t, 3H).

b-H 5-(2,3-Dihydroxypropyl)-6-(dimethylcarbamoyl)-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate

To the solution of citric acid (18.6 g, 96.6 mmol) in a mixture of water (173 ml) an tert.-butanol (173 ml) 5-allyl-6-(dimethylcarbamoyl)-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalat (17.3 g, 48.3 mmol), *N*-methylmorpholine-*N*-oxide (6.22 g, 53.1 mmol), and $K_2OsO_4xH_2O$ (3.55 g, 9.70 mmol) was added. The solution was stirred at room temperature for 18 h. The pH-value was adjusted to 8-9 by adding a saturated solution of sodium bicarbonate. The aqueous mixture was concentrated to one half and, after addition of solid sodium chloride, extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was recrystallized from isopropanol to afford 15 g (79 %) of the title compound as a white solid. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 7.28 (s, 1H), 4.46 (t, 1H), 3.71 (s, 3H), 3.60 (m, 1H), 3.30 (s, 1H), 3.22 (t, 2H), 3.03 (s, 3H), 2.82 (s, 3H), 2.58-2.36 (m, 5H + DMSO), 1.38 (s, 9H).

b-I Ethyl 4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazole-6-carboxylate

The solution of ethyl 5-(2,3-dihydroxypropyl)-4-[(2,2-dimethylpropanoyl)oxy]-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate (12.0 g, 30.57 mmol) in methanol (270 ml) was cooled to 0°C and a solution of $NaIO_4$ (13.1 g, 61.15 mmol) in water (110 ml) was added during a period of 30 min. The solution was stirred for 3 h in which a white precipitate was formed. The reaction mixture was poured onto water (500 ml). The aqueous phase was extracted with dichloromethane, the combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was crystallized using diisopropyl ether to afford 9.83 g (89 %) of the title compound as white crystals which needed no further purification. ^{1}H NMR (d_6-DMSO, 200 MHz): δ = 9.60 (s, 1H), 8.04 (s, 1H), 4.30 (q, 2H), 3.95 (s, 2H), 3.80 (s, 3H), 2.55 (s, 3H), 1.36 (s, 9H), 1.33 (t, 3H).

b-J 6-(Dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate

The suspension of 5-(2,3-dihydroxypropyl)-6-(dimethylcarbamoyl)-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate (28.4 g, 72.54 mmol) in methanol (650 ml) was cooled to 0°C and a solution of $NaIO_4$ (31.0 g, 145.0 mmol) was added during a period of 45 min. The solution was stirred for 2 h in which a white precipitate was formed. Water was added until a solution resulted. The aqueous phase was extracted with dichloromethane, the combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was crystallized using diisopropyl ether to afford 24.32 g (93 %) of the title compound as pale brown crystals which needed no further purification. The ^{1}H-NMR spectrum shows a mixture of the aldehyde and the corresponding enol in a ration 2:3: ^{1}H NMR (d_6-DMSO, 200 MHz): aldehyde-form: δ = 9.50 (s, 1H), 7.41 (s, 1H), 3.74 (s, 3H), 3.55 (d, 2H), 3.01 (s, 3H), 2.82 (s, 3H), 2.54-2.38 (m, 3H + DMSO), 1.35 (s, 9H); enol-form: δ = 7.29 (s, 1H), 6.21 (br s, 1H), 4.51 (q, 1H), 3.71 (s, 3H), 3.13 (s, 1H), 3.03 (s, 3H), 2.83 (s, 3H), 2.54-2.38 (m, 3H + DMSO), 1.38 (s, 9H).

b-K 6-(Dimethylcarbamoyl)-1,2-dimethyl-5-[2-(1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)ethyl]-1*H*-benzimidazol-4-yl pivalate

The solution of 1-indanone (2.17 g, 16.38 mmol) in THF (34 ml) was cooled to –70°C and a solution of lithium bis(trimethylsilyl)amide in THF (16.40 ml, 16.40 mmol; 1N) was added via syringe during a period of 10 min. The solution was stirred for 30 min at this temperature and a solution of 6-(dimethylcarbamoyl)-1,2-dimethyl-5-(2-oxoethyl)-1*H*-benzimidazol-4-yl pivalate (5.90 g, 16.38 mmol) in THF was added slowly. After stirring for 30 min at –70°C and for 30 min at –50°C, the reaction mixture was poured onto a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with dichloromethane, the combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The resulting dark oil was dissolved in acetic acid (120 ml), the mixture was warmed to 60°C and concentrated sulfuric acid (1 ml) was added. After stirring for 30 min at 60°C, the reaction mixture was cooled to room temperature, concentrated in vacuo to one third of the volume, and poured onto a mixture of water and dichloromethane. The mixture was neutralized by adding a saturated aqueous solution of $NaHCO_3$ and extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using toluene:dioxane:methanol (2 : 1 : 0.2, v/v/v) and crystallized with diisopropyl ether and ethyl acetate to afford 1.68 g (21 %) of the title compound. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.83 (d, 1H), 7.65-7.45 (m, 2H), 7.38 (t, 1H), 6.99 (s, 1H), 6.85 (t, 1H), 3.91-3.52 (m, 6H), 2.88 (s, 3H), 2.75 (s, 3H), 2.57 (s, 3H), 1.47 (s, 9H).

b-L 6-(Dimethylcarbamoyl)-1,2-dimethyl-5-[2-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)ethyl]-1*H*-benzimidazol-4-yl pivalate

The solution of 6-(dimethylcarbamoyl)-1,2-dimethyl-5-[2-(1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)ethyl]-1*H*-benzimidazol-4-yl pivalate (1.50 g, 3.16 mmol) in ethyl acetate (350 ml) was treated with platinum(IV) oxide hydrate and hydrogenated under an atmosphere of hydrogen for one hour. The catalyst was filtered off and the filtrate was concentrated in vacuo. The resulting oil was crystallized with diisopropyl ether and ethyl acetate to afford 1.20 g (80 %) of the title compound. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.72 (d, 1H), 7.56 (t, 1H), 7.48-7.13 (m, 2H), 7.03 (s, 1H), 3.65 (s, 3H), 3.32 (dd, 1H), 3.17 (s, 3H), 2.98-2.49 (m, 8H), 2.38-2.02 (m, 2H), 1.97-1.68 (m, 2H).

b-M 6-(Dimethylcarbamoyl)-5-[2-(1-hydroxy-2,3-dihydro-1*H*-inden-2-yl)ethyl]-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate

The solution of 6-(dimethylcarbamoyl)-1,2-dimethyl-5-[2-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)ethyl]-1*H*-benzimidazol-4-yl pivalate (1.05 g, 2.20 mmol) in methanol (15 ml) was cooled to 0°C and treated with $NaBH_4$ (86 mg, 2.21 mmol). After 30 min at 0°C, the reaction mixture was warmed to room temperature and stirred at this temperature for 22 h. The mixture was poured onto water, citric acid (0.42 g, 2.20 mmol) was added, and the aqueous phase was extracted with dichloromethane after neutralization with a saturated aqueous solution of $NaHCO_3$. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The resulting white solid needed no further purification and was used as such in the next step (1.00 g, 95 %). mp = 130-133°C (CH_2Cl_2)

b-N 4-hydroxy-5-[2-(1*H*-inden-2-yl)ethyl]-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide

The solution of 6-(dimethylcarbamoyl)-5-[2-(1-hydroxy-2,3-dihydro-1*H*-inden-2-yl)ethyl]-1,2-dimethyl-1*H*-benzimidazol-4-yl pivalate (3.80 g, 7.90 mmol) in a mixture of acetic acid (38 ml) and concentrated hydrochloric acid (15 ml) was heated to 100°C. After 75 min, the reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was diluted with water. The aqueous mixture was neutralized using 2N NaOH and extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$), the solvent was removed in vacuo, and the residue was dissolved again in dioxane (30 ml). An aqueous solution of LiOH (12 ml, 1N) was added and the mixture was heated at 80°C for one hour, poured onto a saturated aqueous solution of NH_4Cl, and extracted with ethyl acetate. The combined organic phases were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was crystallized with diisopropyl ether to afford 2.00 g (68 %) of the title compound. ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.43-7.02 (m, 4H), 6.68 (s, 1H), 6.58 (s, 1H), 3.65 (s, 3H), 3.39 (s, 2H), 3.14 (s, 3H), 2.97-2.66 (m, 7H), 2.63 (s, 3H).

b-O Ethyl {2-[(triethylsilyl)oxy]-2,3-dihydro-1*H*-inden-2-yl}acetate

Ethyl (2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)acetate (100 g, 0.454 mol) was dissolved in dichloromethane (250 ml). The solution was cooled to 0°C. Imidazole (34 g, 0.499 mol) was added. Triethylsilyl trifluoromethansulfonate (114 ml, 0.499 mol) was added dropwise in 1.5 h. The mixture was allowed to warm to room temperature overnight. Water and dichloromethane were added and the layers were separated. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo yielding a brown oil which was purified by column chromatography on silica gel using ethyl acetate:heptane (0 : 100 to 1.5 : 98.5, v/v). The title compound was obtained as dark brown oil (48.3 g, 32%). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.22-7.08 (m, 4H), 4.07 (q, 2H), 3.18 (dd, 4H), 2.69 (s, 2H), 1.21 (t, 3H), 0.83 (t, 9H), 0.45 (q, 6H).

b-P {2-[(triethylsilyl)oxy]-2,3-dihydro-1*H*-inden-2-yl}acetaldehyde

The solution of ethyl {2-[(triethylsilyl)oxy]-2,3-dihydro-1*H*-inden-2-yl}acetate (56 g, 167 mmol) in dichloromethane (240 ml) was cooled to –78°C. A solution of diisobutylaluminium hydride in toluene (200 ml, 200 mmol, 1M) was added dropwise in 75 min. The mixture was stirred at –78°C for 4 h, was allowed to warm to –50°C and quenched carefully with methanol (15 ml). After stirring for 15 min at this temperature, the reaction mixture was poured onto a saturated aqueous solution of seignette salt (500 ml). Water (1000 ml) and dichloromethane (500 ml) were added and the mixture was stirred for 18 h. The layers were separated. The organic layer was washed twice with a solution of seignette salt and once with water, dried ($MgSO_4$) and concentrated in vacuo yielding an orange oil which was purified by column chromatography on silica gel using toluene. The title compound was obtained as clear oil (36.9 g, 76%). ^1H NMR ($CDCl_3$, 200 MHz): δ = 9.91 (t, 1H), 7.18 (s, 4H), 3.15 (dd, 4H), 2.68 (d, 2H), 0.86 (t, 9H), 0.47 (q, 6H).

b-Q Ethyl-5-[1-hydroxy-2-(2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)ethyl]-1,2-dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-benzimidazole-6-carboxylate

The solution of ethyl 1,2-dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-benzimidazole-6-carboxylate (12.5 g, 52.7 mmol) in dichloromethane (160 ml) was cooled to 10°C and treated with tert. butyl dimethylsilyl trifluoromethansulfonate (12.5 ml, 54.6 mmol) during a period of 15 min. After cooling down to –40°C, a solution of {2-[(triethylsilyl)oxy]-2,3-dihydro-1*H*-inden-2-yl}acetaldehyde (14.3 g, 49.2 mmol) in dichloromethane (20 ml) was added, stirring was continued for 10 min and a solution of boron trifluoride diethyl etherate (13.7 ml, 54.6 mmol, 50%) was added carefully. The reaction mixture was stirred for one hour at –40°C and was allowed to warm to room temperature overnight. After dilution with dichloromethane, the reaction mixture was poured onto a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with dichloromethane, the combined organic phases were washed with a saturated aqueous solution of NH_4Cl, dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel using toluene:dioxane:methanol (20:10:3) and crystallized using ethyl acetate and diisopropyl ether. The title compound was obtained as slightly yellow solid (8.38 g, 41%). ^{1}H NMR (d_6-DMSO, 400 MHz): δ = 7.22-7.03 (m, 4H), 5.09 (d, 1H), 4.71 (s, 1H), 4.13-3.95 (m, 3H), 3.72-3.58 (m, 1H), 3.49 (s, 3H), 3.28-2.68 (m, 7H), 2.29 (s, 3H), 2.02-1.71 (m, 2H), 1.10 (t, 3H).

b-R Ethyl-2,3-dimethyl-1',3'-dihydro-3*H*-spiro[chromeno[7,8-*d*]imidazole-8,2'-indene]-5-carboxylate

The solution of tert. butyl dimethylsilyl trifluoromethansulfonate (2.60 ml, 11.0 mmol) in dichloromethane (10 ml) was added dropwise to the suspension of ethyl 5-[1-hydroxy-2-(2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)ethyl]-1,2-dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-benzimidazole-6-carboxylate (2.27 g, 5.50 mmol) and $MgSO_4$ (4.0 g) in dichloromethane (75 ml). After stirring for 10 min at room temperature, solid 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.89 g, 8.25 mmol) was added. The reaction mixture is stirred at room temperature for 18 h. The solids were filtered off, a saturated aqueous solution of Na_2CO_3 was added to the filtrate, the layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic phases were washed with water, dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was crystallized using diisopropyl ether to afford 0.61 g (30 %) of the title compound as pale brown solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.53 (s, 1H), 7.43 (d, 1H), 7.18 (s, 4H), 5.76 (d, 1H), 4.41 (q, 2H), 3.71 (s, 3H), 3.62 (d, 2H), 3.20 (d, 2H), 2.53 (s, 3H), 1.40 (t, 3H).

Aspect c:

c-I. Final Compounds of the formula 1 according to aspect c

c-1 Ethyl 2,3-dimethyl-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate

To a solution of 1.96 g (5.0 mmol) ethyl 2,3-dimethyl-6-oxo-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate in 27 ml trifluoroacetic acid were added 5.0 ml (31.2 mmol) triethylsilane and the mixture was stirred at 80 °C overnight. The reaction mixture was evaporated and the residue partitioned between saturated aqueous sodium hydrogen carbonate and ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulphate and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, diethyl ether/triethylamine 9:1) and crystallization from ethyl acetate/n-heptane yielded 212 mg (11 %) of the title compound as a colourless solid. m.p. 127 °C.

c-2 *N*,2,3-trimethyl-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxamide

A mixture of 0.38 g (3.4 mmol) potassium tert-butoxide and 145 mg (0.39 mmol) ethyl 2,3-dimethyl-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate in 10 ml tert-butanol was stirred at 45 °C overnight. The reaction mixture was brought to pH ~ 3 by addition of 2N hydrochloric acid and evaporated to dryness. After coevaporation with acetone, the residue was suspended in 10 ml tetrahydrofuran and 130 mg (0.8 mmol) N,N'-carbonyldiimidazole were added. After 30 min, 1 ml (7.5 mmol) methylamine (7.5M in N,N-dimethylformamide) was added and stirring was continued for 20 min. The reaction mixture was partitioned between saturated aqueous ammonium chloride and ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulphate and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, ethyl acetate/triethylamine 9:1) and crystallization from diisopropyl ether yielded 37 mg (26 %) of the title compound as a beige solid. m.p. 296-298 °C.

c-3 *N,N*,2,3-tetramethyl-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxamide

A mixture of 0.45 g (4 mmol) potassium tert-butoxide and 190 mg (0.51 mmol) ethyl 2,3-dimethyl-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate in 14 ml tert-butanol was stirred at 45 °C overnight. The reaction mixture was brought to pH ~ 4 by addition of 4N hydrochloric acid and evaporated. After coevaporation with acetone, the residue was suspended in 14 ml tetrahydrofuran and 245 mg (1.5 mmol) N,N'-carbonyldiimidazole were added. After 1 h, 0.4 ml condensed dimethylamine were added at 0 °C and stirring was continued at room temperature overnight. The reaction mixture was partitioned between saturated aqueous ammonium chloride and dichloromethane. The organic layer was separated, dried over anhydrous magnesium sulphate and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, ethyl ace-

tate/triethylamine 9:1) and crystallization from ethyl acetate/n-heptane yielded 58 mg (30 %) of the title compound as a colourless solid. m.p. 234-235 °C.

c-II. Starting materials for aspect c

c-A N'-(2,3-Dihydro-1*H*-inden-1-ylidene)benzohydrazide

A mixture of 10.0 g (75.7 mmol) 1-indanone and 10.3 g (75.7 mmol) benzoylhydrazine in 90 ml methanol and 1 ml acetic acid was refluxed for 3 h. The reaction mixture was cooled down and evaporated. The residue was crystallized from ethyl acetate/n-heptane to yield 17.3 g (91 %) of the title compound (m.p. 163-166 °C).

c-B N'-(1-Allyl-2,3-dihydro-1*H*-inden-1-yl)benzohydrazide

To a suspension of 3.75 g (15 mmol) N'-(2,3-dihydro-1*H*-inden-1-ylidene)benzohydrazide in 70 ml dried tetrahydrofuran were added 37.5 ml (37.5 mmol) allylmagnesium bromide (1M in diethyl ether) over a period of 20 min at 0 °C. After 1 h at room temperature, saturated aqueous ammonium chloride was added and excess tetrahydrofuran was removed in vacuo. The remaining emulsion was extracted with dichloromethane (4 x). The combined organic layer were dried over anhydrous magnesium sulphate and concentrated in vacuo to give 4.41 g of the title compound as a pale yellow wax. An analytical sample was obtained by crystallization from diethyl ether: m.p. 85-87 °C. ^{1}H-NMR (DMSO), δ (ppm): 1.93-2.26 (m, 2 H), 2.50-2.60 (m, 2 H), 2.65-3.05 (m, 2 H), 4.95-5.15 (m, 2 H), 5.45 (d, 1 H), 5.60-5.85 (m, 1 H), 7.1-7.6 (m, 7 H), 7.65-7.75 (m, 2 H).

c-C 1-Allylindan-1-amine

A solution of 1.0 g (3.4 mmol) N'-(1-allyl-2,3-dihydro-1*H*-inden-1-yl)benzohydrazide in 9 ml dried tetrahydrofuran was slowly added to ~ 30 ml liquid ammonia at -78 °C. To the resulting solution were added 0.16 g (23 mmol) freshly cut lithium until a deep blue colour appeared. The cooling bath was removed and excess ammonia was allowed to evaporate. After 30 min, solid ammonium chloride was carefully added and the mixture was carefully hydrolyzed with water. The mixture was partitioned between water and dichloromethane. The organic layer was separated, dried over anhydrous magnesium sulphate and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, petroleum ether, then petroleum ether/ethyl acetate 3:7) yielded 0.52 g (88 %) of the title compound as a colourless oil. ^{1}H-NMR (DMSO), δ (ppm): 1.81 (ddd, 1 H), 1.9 (bs, 2 H), 2.12 (ddd, 1 H), 2.23-2.42 (m, 2 H), 2.65-3.13 (m, 2 H), 4.98-5.06 (m, 2 H), 5.65-5.86 (m, 1 H), 7.14-7.30 (m, 4H).

c-D tert-Butyl (1-allyl-2,3-dihydro-1*H*-inden-1-yl)carbamate

To a suspension of 0.2 g (1.15 mmol) 1-allylindan-1-amine 2 ml dioxane and 1 ml water were added 0.3 g (1.38 mmol) di-tert-butyl dicarbonate at 0 °C. After 2 h stirring at room temperature, water was added and the mixture was extracted with diethyl ether (4 x). The organic layer was separated, dried over anhydrous magnesium sulphate and concentrated in vacuo. Purification of the residue by column

chromatography (silica gel, petroleum ether/ethyl acetate 9:1) yielded 0.28 g (88 %) of the title compound as a colourless oil. ^{1}H-NMR (DMSO), δ (ppm): 1.3 (br s, 9 H), 1.9-2.5 (m, 3 H), 2.6-3.0 (m, 3 H), 4.9-5.1 (m, 2 H), 5.5-5.8 (m, 1 H), 6.8 (bs, 1 H), 7.1-7.4 (m, 4H).

c-E {1-[(tert-Butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}acetic acid

To a solution of 4.5 g (16.5 mol) tert-butyl (1-allyl-2,3-dihydro-1*H*-inden-1-yl)carbamate in 34 ml carbon tetrachloride were added 34 ml acetonitrile, 50 ml water, 14.5 g (67.7 mmol) sodium (meta)periodate and 0.34 g (1.65 mmol) ruthenium(III) chloride hydrate. After 18 h stirring at room temperature, 200 ml water and 150 ml dichloromethane were added and the mixture was filtered through Celite. The filtrate was extracted with dichloromethane (5 x 100 ml) and the combined organic layers were dried over anhydrous magnesium sulphate and evaporated. Purification of the residue by column chromatography (silica gel, petroleum ether/ethyl acetate 1:1) yielded 3.65 g (76 %) of the title compound as a colourless oil. ^{1}H-NMR ($CDCl_3$), δ (ppm): 1.35 (br s, 9 H), 2.4-2.6 (m, 2 H), 2.8-3.2 (m, 4 H), 7.15-7.35 (m, 4H).

c-F Ethyl {1-[(tert-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}acetate

To a solution of 3.32 g (11.4 mmol) {1-[(tert-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}acetic acid in 37 ml N,N-dimethylformamide were added 2.51 g (25.1 mmol) potassium hydrogen carbonate. After 45 min, 1.0 ml (12.5 mmol) ethyl iodide was added and the mixture was stirred 4 h at room temperature. The mixture was diluted with 200 ml ethyl acetate and the organic layer was washed successively with water (2 x 50 ml), 0.5 ml acetic acid in 50 ml brine and saturated aqueous ammonium chloride (2 x 50 ml). The organic layer was dried over anhydrous magnesium sulphate and the volatiles were removed in vacuo to leave 3.12 g (86 %) of the title compound as a light yellow oil. ^{1}H-NMR ($CDCl_3$), δ (ppm): 1.17 (t, 3 H), 1.37 (br s, 9 H), 2.32-2.65 (m, 2 H), 2.78-3.07 (m, 4 H), 4.10 (q, 2 H), 5.51 (br s, 1 H), 7.16-7.31 (m, 4H).

c-G Ethyl (1-amino-2,3-dihydro-1*H*-inden-1-yl)acetate

To a solution of 6.1 ml (86 mmol) acetyl chloride in 30 ml dried ethanol was slowly added a solution of 3.02 g (9.5 mmol) ethyl {1-[(tert-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}acetate in 14 ml ethanol. After 5d at room temperature, the reaction mixture was slowly dropped into 300 ml saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the combined organic layers were dried over anhydrous magnesium sulphate and evaporated. Purification of the residue by column chromatography (silica gel, petroleum ether/ethyl acetate 1:1, then ethyl acetate) yielded 1.32 g (63 %) of the title compound as a light yellow oil. ^{1}H-NMR ($CDCl_3$), δ (ppm): 1.23 (t, 3 H), 1.97-2.12 (m, 1 H), 2.1 (br s, 2 H), 2.30-2.42 (m, 1 H), 2.67 (br q, 2 H), 2.81-3.04 (m, 2 H), 4.13 (q, 2 H), 7.17-7.35 (m, 4 H).

c-H (2*R*)-2-[2,3-Dihydro-1*H*-inden-1-ylideneamino]-2-phenylacetamide

To a suspension of 103.6 g (0.69 mol) (2*R*)-2-amino-2-phenylacetamide in 500 ml isopropyl acetate were added 100.3 g (0.76 mol) 1-indanone and 6.6 g (5 mol%) p-toluenesulphonic acid monohydrate.

The mixture was boiled under reflux during which ~ 10 ml of solvent was removed from the fitted Dean-Stark trap hourly. After 6 h, the expected amount of water had distilled off and the reaction mixture was allowed to cool to room temperature after which it was filtered. The collected solid was stirred in 500 ml water for 5 min and then filtered. The residue was washed with isopropyl acetate (2 x 250 ml) and dried in vacuo to give 134.7 g (74 %) of the title compound as a colourless solid. ^{1}H-NMR ($CDCl_3$), δ (ppm): 2.4-2.6 (m, 1 H), 2.8-3.0 (m, 1 H), 3.1-3.2 (m, 2 H), 5.1 (s, 1 H), 6.0 (br s, 1 H), 7.4-7.6 (m, 8 H), 7.7 (br s, 1 H), 8.0 (d, 1 H).

c-I (2*R*)-2-{[(1*R*)-1-Allyl-2,3-dihydro-1*H*-inden-1-yl]amino}-2-phenylacetamide

To a solution of allylzinc bromide in 800 ml tetrahydrofuran [prepared from 30.3 g (0.46 mol) zinc granules and 65.8 g (0.54 mol) allyl bromide] were added 81.7 g (0.31 mol) (2*R*)-2-[2,3-dihydro-1*H*-inden-1-ylideneamino]-2-phenylacetamide in small portions at -10 °C. After complete addition, the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then poured into 800 ml saturated aqueous ammonium chloride and filtered through Celite. The filtrate was dried over sodium sulphate and the volatiles were removed in vacuo. The remaining oil was partitioned between 500 ml dichloromethane and 250 ml water and filtered through Celite. The organic layer was separated, dried over sodium sulphate and concentrated in vacuo to give 65.9 g (70 %) of the title compound as an orange oil. ^{1}H-NMR ($CDCl_3$), δ (ppm): 2.1 (m, 2 H), 2.2 (br s, 1 H), 2.4-2.6 (m, 3 H), 2.8-3.0 (m, 2 H), 4.0 (s, 1 H), 5.1 (m, 2 H), 5.7 (m, 1 H), 6.4 (br s, 1 H), 7.0 (d, 1 H), 7.1-7.4 (m, 8 H), 7.6 (br s, 1 H).

c-J (1*R*)-1-Allylindan-1-amine

To a solution of 85.0 g (0.28 mol) (2*R*)-2-{[(1*R*)-1-allyl-2,3-dihydro-1*H*-inden-1-yl]amino}-2-phenylacetamide in 425 ml dichloromethane were added 195 ml triethylamine. The mixture was cooled to -20 °C and 57 ml (0.62 mol) phosphoryl chloride were added dropwise at such a rate that the temperature did not rise above -15 °C. After complete addition, the mixture was allowed to warm to room temperature, stirred for 1 h and poured onto 600 g of crushed ice. The pH was adjusted to 9 with 10% aqueous sodium hydroxide. The layers were separated and the aqueous layer was extracted with dichloromethane (200 ml). The combined organic layers were dried over sodium sulphate and the volatiles were removed in vacuo. The resulting brown oil (~ 85 g) was dissolved in 425 ml ethanol and 82.0 g (0.59 mol) potassium carbonate were added. The mixture was refluxed for 2 h after which the solvent was removed in vacuo. The residue was partitioned between 400 ml dichloromethane and 400 ml water, the layers were separated and the aqueous layer was extracted with dichloromethane (100 ml). The combined organic layers were dried over sodium sulphate and the volatiles were removed in vacuo. The resulting brown oil (~ 71 g) was dissolved in 350 ml tetrahydrofuran/water 1:1 and 57 g (0.82 mol) hydroxylamine hydrochloride were added. After stirring the mixture for 5 h, the pH was adjusted to 1 with 1N hydrochloric acid and the volatiles were removed in vacuo. The remaining emulsion was diluted with 250 ml tert-butyl methyl ether and washed with water (2 x 250 ml). The pH of the combined aqueous layer was adjusted to 10 with 10% aqueous sodium hydroxide and extracted with dichloromethane (2 x 200 ml). The combined organic layers were dried over sodium sulphate and the

volatiles were removed in vacuo. The resulting brown oil (37.4 g) was purified by Kugelrohr distillation (80-90 °C, 0.01 Torr) to give 30.8 g (64 %) of the title compound as a colourless oil. ^{1}H-NMR ($CDCl_3$), δ (ppm): 1.6 (br s, 2 H), 1.9 (m, 1 H), 2.3 (m, 1 H), 2.4 (m, 2 H), 2.8-3.0 (m, 2 H), 5.1 (m, 2 H), 5.8 (m, 1 H), 7.2 (m, 4H).

c-K tert-Butyl [(1*R*)-1-allyl-2,3-dihydro-1*H*-inden-1-yl]carbamate

To a solution of 30.0 g (0.17 mol) (1*R*)-1-allylindan-1-amine in 500 ml 1N aqueous sodium hydroxide and 250 ml tert-butanol were added 57.0 g (0.26 mol) di-tert-butyl dicarbonate in portions. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. After addition of 250 ml saturated aqueous ammonium chloride, the mixture was extracted with tert-butyl methyl ether (2 x 250 ml). The combined organic layers were washed successively with 1N hydrochloric acid, saturated aqueous sodium carbonate and brine. The combined organic layers were dried over sodium sulphate and the volatiles were removed in vacuo to leave 33.9 g (72 %) of the title compound as an orange oil. ^{1}H-NMR ($CDCl_3$), δ (ppm): 1.6 (br s, 9 H), 2.4-3.0 (m, 6 H), 5.0 (s, 1 H), 5.2 (m, 2 H), 5.8 (m, 1 H), 7.3 (m, 4H).

c-L {(1*R*)-1-[(tert-Butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}acetic acid

To a solution of 239.0 g (1.12 mol) sodium (meta)periodate in 4 l water were added 3.9 g (25 mmol) potassium permanganate, 19.0 g (138 mmol) potassium carbonate and 1 l tert-butanol in succession. A solution of 33.9 g (0.12 mol) tert-butyl [(1*R*)-1-allyl-2,3-dihydro-1*H*-inden-1-yl]carbamate in 1 l tert-butanol was added dropwise, during which the colour changed from deep purple to pink. The mixture was stirred for 3 h, then 31 ml ethylene glycol were added dropwise. The mixture was stirred for an additional 3 h, then the pH was adjusted to 1 with 10% hydrochloric acid. The suspension was filtered and tert-butanol was removed from the filtrate in vacuo. The residue was extracted with ethyl acetate (2 x 500 ml), the combined organic layers were washed with brine (250 ml) and dried over sodium sulphate. The volatiles were removed in vacuo to leave 26.1 g (72 %) of the title compound as a brown oil.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.4 (br s, 9 H), 2.4-2.6 (m, 2 H), 2.8-3.1 (m, 4 H), 7.2-7.4 (m, 4H), 9.0 (br s, 1 H).

c-M Ethyl {(1*R*)-1-[(tert-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}acetate

To a solution of 22.5 g (77.2 mmol) {(1*R*)-1-[(tert-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}acetic acid in 250 ml N,N-dimethylformamide were added 17.0 g (0.17 mol) potassium hydrogen carbonate. After 45 min, 6.8 ml (85 mmol) ethyl iodide were added and the mixture was stirred overnight at ambient temperature. The mixture was poured into 750 ml ethyl acetate and the organic layer was washed with water (5 x 500 ml), 0.5M acetic acid (500 ml) combined with brine and saturated aqueous ammonium chloride (500 ml). The organic layer was dried over sodium sulphate and the volatiles were removed in vacuo to leave 21.1 g (86 %) of the title compound as a brown oil. ^{1}H-NMR ($CDCl_3$), δ (ppm): 1.3 (t, 3 H), 1.4 (br s, 9 H), 2.4-2.7 (m, 2 H), 2.9-3.2 (m, 4 H), 4.2 (q, 2 H), 5.7 (br s, 1 H), 7.2-7.4 (m, 4H).

c-N Ethyl [(1*R*)-1-amino-2,3-dihydro-1*H*-inden-1-yl]acetate

To a solution of 22.3 g (66 mmol) ethyl {(1*R*)-1-[(tert-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}acetate in 100 ml ethanol were added dropwise 250 ml 2.5M hydrogen chloride in ethanol. The mixture was stirred 3 d, then the volatiles were removed in vacuo. The residue was partitioned between 100 ml tert-butyl methyl ether and 100 ml water and the organic layer was extracted with water (100 ml). The pH of the combined aqueous layers was adjusted to 10 with 10% aqueous sodium hydroxide. The aqueous layer was extracted with dichloromethane (75 ml), the combined organic layers were dried over sodium sulphate and the volatiles were removed in vacuo. The resulting brown oil (10 g) was purified by Kugelrohr distillation (100-130 °C, 0.04 Torr) to give 8.4 g (55 %) of the title compound as a yellow oil, which darkened on standing. ^{1}H-NMR ($CDCl_3$), δ (ppm): 1.2 (t, 3 H), 2.0 (m, 1 H), 2.1 (br s, 2 H), 2.4 (m, 1 H), 2.6-2.8 (br q, 2 H), 2.8-3.0 (m, 2 H), 4.1 (q, 2 H), 7.2 (m, 3 H), 7.3 (m, 1H). GC-MS: 97 % purity. HPLC (Chiralcel OD-H): 88 % ee.

c-O Ethyl [(1*S*)-1-amino-2,3-dihydro-1*H*-inden-1-yl]acetate

The title compound was prepared analogously to the (R)-enantiomer following the steps described in examples H - N, but starting from (2*S*)-2-amino-2-phenylacetamide.

c-P Ethyl (8*R*)-2,3-dimethyl-6-oxo-2',3,3',4,5,6,7,9-octahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate, mixture of (5*S*,8*R*)- and (5*R*,8*R*)-isomers

A mixture of 4.0 g (17 mmol) ethyl 1,2-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-benzimidazole-6-carboxylate, 4.8 g (22 mmol) ethyl [(1*R*)-1-amino-2,3-dihydro-1*H*-inden-1-yl]acetate and 100 mg p-toluenesulphonic acid monohydrate in 100 ml xylene was heated on a Dean-Stark trap. After 3 d, an additional 1.0 g (4.6 mmol) ethyl [(1*R*)-1-amino-2,3-dihydro-1*H*-inden-1-yl]acetate were added and heating was continued for 1 d. The reaction mixture was cooled down and evaporated to dryness. The residue was purified by column chromatography (silica gel, toluene/dioxane/methanol 7:2.5:0.5) to yield 1.96 g (29 %) of the title compound as a foam.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.20-1.27 (m, 3 H), 2.19-2.40 (m, 1 H), 2.36 (s, 3 H), 2.51-2.61 (m, 1 H), 2.81-3.06 (m, 5 H), 3.31-3.39 (m, 1 H), 3.51 (s, 3 H), 4.07-4.14 (m, 2 H), 4.26-4.30 (m, 1 H), 5.94, 5.98 (2 br s, 1 H), 7.14-7.56 (m, 4 H).

c-Q Ethyl (8*R*)-2,3-dimethyl-6-oxo-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate

To a solution of 1.85 g (4.7 mmol) ethyl (8*R*)-2,3-dimethyl-6-oxo-2',3,3',4,5,6,7,9-octahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate [mixture of (5*S*,8*R*)- and (5*R*,8*R*)-isomers] in 70 ml ethyl acetate were added 1.14 g (5.0 mmol) 2,3-dichloro-5,6-dicyanobenzoquinone. After complete reaction (30 min), the mixture was partitioned between saturated aqueous sodium hydrogen carbonate and ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulphate and concentrated in vacuo. Purification of the residue by column chromatography (silica

gel, toluene/dioxane/methanol 6:3.5:0.5) and crystallization from ethyl acetate/n-heptane yielded 1.24 g (68 %) of the title compound as a colourless solid. m.p. 212-213 °C. HPLC (Chiralcel OD-H): 78 % ee.

c-R Ethyl (8*S*)-2,3-dimethyl-6-oxo-2',3,3',4,5,6,7,9-octahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate, mixture of (5*S*,8*S*)- and (5*R*,8*S*)-isomers

The title compound was prepared analogously to example H, starting from 5.3 g (22.4 mmol) ethyl 1,2-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-benzimidazole-6-carboxylate and 5.9 g (26.9 mmol) ethyl [(1*S*)-1-amino-2,3-dihydro-1*H*-inden-1-yl]acetate. Yield: 0.94 g (11 %), colourless oil.

c-S Ethyl-(8*S*)-2,3-dimethyl-6-oxo-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate

The title compound was prepared analogously to example I, starting from 0.94 g (2.4 mmol) ethyl (8*S*)-2,3-dimethyl-6-oxo-2',3,3',4,5,6,7,9-octahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate [mixture of (5*S*,8*S*)- and (5*R*,8*S*)-isomers] and 0.6 g (2.64 mmol) 2,3-dichloro-5,6-dicyanobenzoquinone. Yield: 0.45 g (48 %). HPLC (Chiralcel OD-H): 78 % ee.

c-T Ethyl_2,3-dimethyl-6-oxo-2',3,3',4,5,6,7,9-octahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate, mixture of *rel*-(5*S*,8*S*)- and *rel*-(5*R*,8*S*)-isomers

The title compound was prepared analogously to example H, starting from 10.0 g (42.3 mmol) ethyl 1,2-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-benzimidazole-6-carboxylate and 11.1 g (50.8 mmol) ethyl (1-amino-2,3-dihydro-1*H*-inden-1-yl)acetate. Yield: 7.59 g (46 %), yellowish foam.

c-U Ethyl-2,3-dimethyl-6-oxo-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate

The title compound was prepared analogously to example I, starting from 7.59 g (19.4 mmol) ethyl 2,3-dimethyl-6-oxo-2',3,3',4,5,6,7,9-octahydrospiro[imidazo[4,5-*h*]quinoline-8,1'-indene]-5-carboxylate [mixture of *rel*-(5*S*,8*S*)- and *rel*-(5*R*,8*S*)-isomers] and 4.88 g (21.5 mmol) 2,3-dichloro-5,6-dicyanobenzoquinone. Yield: 4.8 g (64 %). m.p. 238 °C.

Industrial applicability

The compounds of the formulae 1, 1-a, 1-b, 1-c, 1-a-1, 1-a-2, 1-a-3, 1-a-4, 1-a-5, 1-a-6, 1-b-1, 1-b-2, 1-b-3, 1-b-4, 1-c-1, 1-c-2, 1-c-3, 1-c-4, 1-c-5, 1-c-6, 1-a-1-a, 1-a-2-a, 1-a-3-a, 1-a-4-a, 1-a-5-a, 1-a-6-a, 1-a-1-b, 1-a-2-b, 1-a-3-b, 1-a-4-b, 1-a-5-b, 1-a-6-b, 1-b-1-a, 1-b-2-a, 1-b-3-a, 1-b-4-a, 1-b-1-b, 1-b-2-b, 1-b-3-b, 1-b-4-b, 1-c-1-a, 1-c-2-a, 1-c-3-a, 1-c-4-a, 1-c-5-a, 1-c-6-a, 1-c-1-b, 1-c-2-b, 1-c-3-b, 1-c-4-b, 1-c-5-b and 1-c-6-b and their pharmaceutically acceptable salts (= active compounds according to the invention) have valuable pharmacological properties which make them commercially utilizable. In particular, they exhibit marked inhibition of gastric acid secretion and an excellent gastric and intestinal protective or curative action in warm-blooded animals, in particular humans. In this connection, the active compounds according to the invention are distinguished by a high selectivity of action, a fast onset of action, an advantageous duration of action, efficient control of the duration of action by the dosage, a particularly good antisecretory efficacy, the absence of significant side effects and a large therapeutic range.

Compared to compounds known from the prior art, the compounds according to the present invention are particularly distinguished by a more favorable interaction with other biologic targets such as ion channels or other enzymes.

“Gastric and intestinal protection or cure” in this connection is understood to include, according to general knowledge, the prevention, the treatment and the maintenance treatment of gastrointestinal diseases, in particular of gastrointestinal inflammatory diseases and lesions (such as, for example, reflux esophagitis, gastritis, hyperacidic or drug-related functional dyspepsia, and peptic ulcer disease [including peptic ulcer bleeding, gastric ulcer, duodenal ulcer]), which can be caused, for example, by microorganisms (e.g. Helicobacter pylori), bacterial toxins, drugs (e.g. certain antiinflammatories and antirheumatics, such as NSAIDs and COX-inhibitors), chemicals (e.g. ethanol), gastric acid or stress situations.

The term “gastrointestinal diseases” is understood to include, according to general knowledge,

A) gastroesophageal reflux disease (GERD), the symptoms of which include, but are not limited to, heartburn and/or acid regurgitation and/or non-acid regurgitation.

B) other extra-esophageal manifestations of GERD that include, but are not limited to, acid-related asthma, bronchitis, laryngitis and sleep disorders.

C) other diseases that can be connected to undiagnosed reflux and/or aspiration include, but are not limited to, airway disorders such as asthma, bronchitis, COPD (chronic obstructive pulmonary disease).

D) Helicobacter pylori infection whose eradication is playing a key role in the treatment of gastrointestinal diseases.

E) Furthermore, “gastrointestinal diseases” comprise other gastrointestinal conditions that might be related to acid secretion, such as Zollinger-Ellison syndrome, acute upper gastrointestinal bleeding, nausea, vomiting due to chemotherapy or post-operative conditions, stress ulceration, IBD (inflammatory bowel disease) and particularly IBS (irritable bowel syndrome).

In their excellent properties, the active compounds according to the invention surprisingly prove to be clearly superior to the compounds known from the prior art in various models in which the antiulcerogenic and the antisecretory properties are determined. On account of these properties, the active compounds according to the invention are outstandingly suitable for use in human and veterinary medicine, where they are used, in particular, for the treatment and/or prophylaxis of disorders of the stomach and/or intestine and/or upper digestive tract, particularly of the abovementioned diseases.

A further subject of the invention are therefore the active compounds according to the invention for use in the treatment and/or prophylaxis of the abovementioned diseases.

The invention likewise includes the use of the active compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the abovementioned diseases.

The invention furthermore includes the use of the active compounds according to the invention for the treatment and/or prophylaxis of the abovementioned diseases.

A further subject of the invention are medicaments which comprise one or more active compounds according to the invention.

As medicaments, the active compounds according to the invention are either employed as such, or preferably in combination with suitable pharmaceutical excipients in the form of tablets, coated tablets (e.g. film-coated tablets), multi unit particulate system tablets, capsules, suppositories, granules, powders (e.g. lyophilized compounds), pellets, patches (e.g. as TTS [transdermal therapeutic system]), emulsions, suspensions or solutions. The content of the active compound is advantageously being between 0.1 and 95wt% (weight percent in the final dosage form), preferably between 1 and 60wt%. By means of the appropriate selection of the excipients, it is possible to obtain a pharmaceutical administration form adapted to the active compound and/or to the desired onset and/or duration of action (e.g. a sustained release form or a delayed release form).

The active compounds according to the invention can be administered orally, parenterally (e.g. intravenously), rectally or percutaneously. Oral or intravenous administration is preferred.

The excipients or combinations of excipients which are suitable for the desired pharmaceutical formulations are known to the person skilled in the art on the basis of his/her expert knowledge and are

composed of one or more accessory ingredients. In addition to solvents, antioxidants, stabilizers, surfactants, complexing agents (e.g. cyclodextrins), the following excipients may be mentioned as examples: For oral administration, gelling agents, antifoams, plasticizer, adsorbent agents, wetting agents, colorants, flavorings, sweeteners and/or tabletting excipients (e.g. carriers, fillers, binders, disintegrating agents, lubricants, coating agents); for intravenous administration, dispersants, emulsifiers, preservatives, solubilizers, buffer substances and/or isotonic adjusting substances. For percutaneous administration, the person skilled in the art may choose as excipients, for example: solvents, gelling agents, polymers, permeation promoters, adhesives, matrix substances and/or wetting agents.

In general, it has been proven advantageous in human medicine to administer the active compound(s) in the case of oral administration in a daily dose (given continuously or on-demand) of approximately 0.01 to approximately 20, preferably 0.02 to 5, in particular 0.02 to 1.5, mg/kg of body weight, if appropriate in the form of several, preferably 1 to 2, individual doses to achieve the desired result. In the case of a parenteral treatment, similar or (in particular in the case of the intravenous administration of the active compounds), as a rule, lower doses can be used. Furthermore, the frequency of administration can be adapted to intermittent, weekly, monthly, even more infrequent (e.g. implant) dosing. The establishment of the optimal dose and manner of administration of the active compounds necessary in each case can easily be carried out by any person skilled in the art on the basis of his/her expert knowledge.

The medicaments may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmaceutical science. All methods include the step of bringing the active compounds according to the invention into association with the excipients or a combination of excipients. In general the formulations are prepared by uniformly and intimately bringing into association the active compounds according to the invention with liquid excipients or finely divided solid excipients or both and then, if necessary, formulating the product into the desired medicament.

The active compounds according to the invention or their pharmaceutical preparations can also be used in combination with one or more pharmacologically active constituents from other groups of drugs [combination partner(s)]. “Combination” is understood to be the supply of both the active compound(s) according to the invention and the combination partner(s) for separate, sequential, simultaneous or chronologically staggered use. A combination is usually designed with the aim of increasing the principal action in an additive or super-additive sense and/or of eliminating or decreasing the side effects of the combination partner(s), or with the aim to obtain a more rapid onset of action and a fast symptom relief. By choosing the appropriate pharmaceutical formulation of the drugs contained in the combination, the drug release profile of the components can be exactly adapted to the desired effect, e.g. the release of one compound and its onset of action is chronologically previous to the release of the other compound.

A combination can be, for example, a composition containing all active compounds (for example a fixed combination) or a kit-of-parts comprising separate preparations of all active compounds.

A “fixed combination” is defined as a combination wherein a first active ingredient and a second active ingredient are present together in one unit dosage or in a single entity. One example of a “fixed combination” is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in admixture of simultaneous administration, such as in a formulation. Another example of a “fixed combination” is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in one unit without being in admixture.

A “kit-of-parts” is defined as a combination wherein the said first active ingredient and the said second active ingredient are present in more than one unit. One example of a “kit-of-parts” is a combination wherein the said first active ingredient and the said second active ingredient are present separately. The components of the kit-of-parts may be administered separately, sequentially, simultaneously or chronologically staggered.

“Other groups of drugs” are understood to include, for example: tranquillizers (for example from the group of the benzodiazepines, like diazepam), spasmolytics (for example butylscopolaminium bromide [Buscopan®]), anticholinergics (for example atropine sulfate, pirenzepine, tolterodine), pain perception reducing or normalizing agents (for example, paracetamol, tetracaine or procaine or especially oxetacain), and, if appropriate, also enzymes, vitamins, trace elements or amino acids.

To be emphasized in this connection is in particular the combination of the active compounds according to the invention with pharmaceuticals which buffer or neutralize gastric acid (such as, for example, magaldrat, aluminium hydroxide, magnesium carbonate, magnesium hydroxide or other antacids), or especially with pharmaceuticals which inhibit or reduce acid secretion, such as, for example:

(I) histamine-H2 blockers [e.g. cimetidine, ranitidine], or

(II) proton pump inhibitors [e.g. omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, tenatoprazole, ilaprazole, leminoprazole, all including their salts and enantiomers] or

(III) other potassium-competitive acid blockers [e.g. soraprazan and its stereoisomers, linaprazan, revaprazan, all including their salts]), or

(IV) so-called peripheral anticholinergics (e.g. pirenzepine), with gastrin antagonists such as CCK2 antagonists (cholestocystokinin 2 receptor antagonists).

An important combination to be mentioned is the combination with antibacterially active substances, and especially substances with a bactericidal effect, or combinations thereof. These combination partner(s) are especially useful for the control of Helicobacter pylori infection whose eradication is playing a key role in the treatment of gastrointestinal diseases. As suitable antibacterially active combination partner(s) may be mentioned, for example:

(A) cephalosporins, such as, for example, cifuroximaxetil

(B) penicillines, such as, for example, amoxicillin, ampicillin

(C) tetracyclines, such as, for example, tetracyline itself, doxycycline

(D) β-lactamase inhibitors, such as, for example, clavulanic acid

(E) macrolide antibiotics, such as, for example, erythromycin, clarithromycin, azithromycin

(F) rifamycines, such as, for example, rifamycine itself

(G) glycoside antibiotics, such as, for example, gentamicin, streptomycin

(H) gyrase inhibitors, such as, for example, ciprofloxaxin, gatifloxacin, moxifloxacin

(I) oxazolidines, such as, for example, linezolid

(J) nitrofuranes or nitroimidazoles, such as, for example, metronidazole, tinidazole, nitrofurantoin

(K) bismuth salts, such as, for example, bismuth subcitrat

(L) other antibacterially active substances

and combinations of substances selected from (A) to (L), for example clarithromycin + metronidazole. Preferred is the use of two combination partners. Preferred is the use of two combination partners selected from amoxicillin, clarithromycin and metronidazole. A preferred example is the use of amoxicillin and clarithromycin.

In view of their excellent activity regarding gastric and intestinal protection or cure, the active compounds according to the invention are especially suited for a free or fixed combination with drugs, which are known to cause “drug-induced dyspepsia” or are known to have a certain ulcerogenic potency, such as, for example, acetylsalicylic acid, certain antiinflammatories and antirheumatics, such as NSAIDs (non-steroidal antiinflammatory drugs, e.g. etofenamate, diclofenac, indometacin, ibuprofen, piroxicam, naproxen, meloxicam), oral steroids, bisphosponates (e.g. alendronate), or even NO-releasing NSAIDs, COX-2 inhibitors (e.g. celecoxib, lumiracoxib).

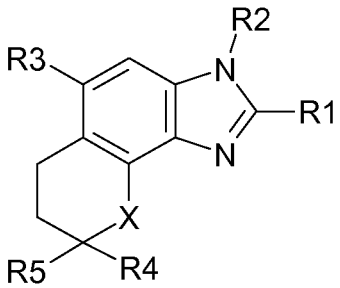
In addition, the active compounds according to the invention are suited for a free or fixed combination with motility-modifying or -regulating drugs (e.g. gastroprokinetics like mosapride, tegaserod, itopride, metoclopramid), and especially with pharmaceuticals which reduce or normalize the incidence of transient lower esophageal sphincter relaxation (TLESR), such as, for example, GABA-B agonists (e.g. baclofen, (2R)-3-amino-2-fluoropropylphosphinic acid) or allosteric GABA-B agonists (e.g. 3,5-bis(1,1-dimethylethyl)-4-hydroxy-β,β-dimethylbenzenepropanol), GABA re-uptake inhibitors (e.g. tiagabine), metabotropic glutamate receptor type 5 (mGluR5) antagonists (e.g. 2-methyl-6-(phenylethynyl)pyridine hydrochloride), CB1 (cannabinoid receptor) agonists (e.g. [(3R)-2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3,de]-1,4-benzoxazin-6-yl]-1-naphthalenyl-methanone mesylate). Pharmaceuticals used for the treatment of IBS or IBD are also suitable combination partner(s), such as, for example: 5-HT4 receptor agonists like mosapride, tegaserod; 5-HT3 receptor antagonists like alosetron, cilansetron; NK2 antagonists like saredutant, nepadutant; κ-opiate agonists like fedotozine.

Suitable combination partner(s) also comprise airway therapeutica, for example for the treatment of acid-related asthma and bronchitis. In some cases, the use of a hypnotic aid (such as, for example,

Zolpidem [Bikalm®]) as combination partner(s) may be rational, for example for the treatment of GERD-induced sleep disorders.

We claim:

1. A compound of the formula 1



(1)

in which

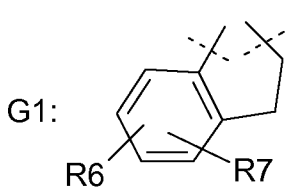
R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or hydroxy-1-4C-alkyl,

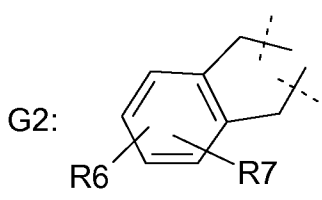
R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl or fluoro-1-4C-alkyl,

R3 is hydrogen, halogen, cyano, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,
or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R4 and R5 together form either a group G1 or a group G2





R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, trifluoromethyl, halo-1-4C-alkoxy, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

X is O or NH

and its salts,

with the proviso that X does not have the meaning NH when R4 and R5 together form a group G2.

2. A compound of the formula 1 as claimed in claim 1, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

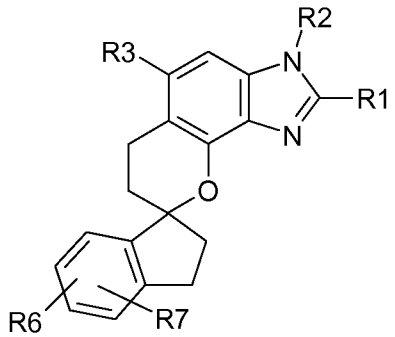
R4 and R5 together form either a group G1 or a group G2

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

and its salts,

with the proviso that X does not have the meaning NH when R4 and R5 together form a group G2.

3. A compound of the formula 1 as claimed in claim 1, characterized by the formula 1-a,



(1-a)

in which

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or fluoro-1-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

R31 is hydrogen, hydroxyl, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, 1-4C-alkoxy, halogen, trifluoromethyl or halo-1-4C-alkoxy,

and its salts.

4. A compound of the formula 1-a as claimed in claim 3,

in which

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-

4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, aziridino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or halo-1-4C-alkoxy,

and its salts.

5. A compound of the formula 1-a as claimed in claim 3,

in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl in which the 1-4C-alkyl is substituted by phenyl, carboxy-1-4-C-alkyl in which the 1-4C-alkyl is substituted by phenyl, fluoro-1-4C-alkyl or 3-7C-cycloalkyl,

R32 is hydrogen or 1-7C-alkyl,

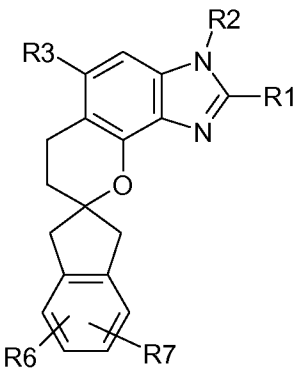
or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, morpholino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

and its salts.

6. A compound of the formula 1 as claimed in claim 1, characterized by the formula 1-b,



(1-b)

in which

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or fluoro-1-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

R31 is hydrogen, hydroxyl, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, 1-4C-alkoxy, halogen, trifluoromethyl or halo-1-4C-alkoxy,

and its salts.

7. A compound of the formula 1-b as claimed in claim 6,

in which

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, aziridino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or halo-1-4C-alkoxy,

and its salts.

8. A compound of the formula 1-b as claimed in claim 6,

in which

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

R31 is 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl

R32 is hydrogen or 1-7C-alkyl,

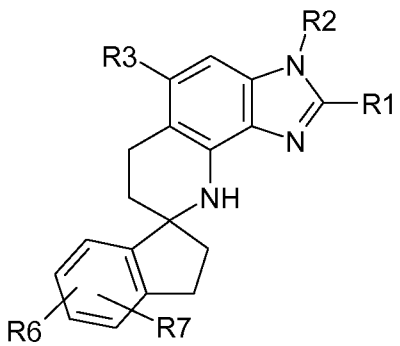
or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, azetidino, isoxazolidino, tetrahydro-1,2-oxazino or 3-(1-4C-alkoxy)azetidino group,

R6 and R7 are each hydrogen,

and its salts.

9. A compound of the formula 1 as claimed in claim 1, characterized by the formula 1-c,



(1-c)

in which

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or fluoro-1-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,
R6 and R7 are identical or different substituents selected from the group consisting of hydrogen,1-4C-alkyl, 1-4C-alkoxy, halogen, trifluoromethyl or halo-1-4C-alkoxy,
and its salts.

10. A compound of the formula 1-c as claimed in claim 9,
in which
R1 is 1-4C-alkyl,
R2 is hydrogen or 1-4C-alkyl,
R3 is carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,
where
R31 is hydrogen, 1-4C-alkoxy, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkyl, 1-4C-alkyl-thio-1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl
R32 is hydrogen or 1-7C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, 4-hydroxypiperidino, azetidino, aziridino, morpholino, isoxazolidino, tetrahydro-1,2-oxazino, 3-fluorazetidino, 3,3-difluorazetidino or 3-(1-4C-alkoxy)azetidino group,
R6 and R7 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or halo-1-4C-alkoxy,
and its salts.

11. A compound of the formula 1-c as claimed in claim 9,
in which
R1 is 1-4C-alkyl,
R2 is 1-4C-alkyl,

R3 is 1-4C-alkoxycarbonyl or the group -CO-NR31R32,
where
R31 is 1-7C-alkyl,
R32 is hydrogen or 1-7C-alkyl,
R6 and R7 are each hydrogen,
and its salts.

12. A compound of the formula 1 as claimed in claim 1, which is selected from the group consisting of
Ethyl 2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxylate,
N,N,2,3,6'-Pentamethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
5'-Fluoro-N,N,2,3-tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
Ethyl-5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxylate,
6'-Fluoro-N,N,2,3-tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
6'-Methoxy-N,N,2,3-tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
7'-Methoxy-N,N,2,3-tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
5'-Chloro-N,N,2,3-tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
N,N,2,3,5'-Pentamethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
5'-Methoxy-N,N,2,3-tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
2,3-Dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxylic acid,
N,N,2,3-Tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
(+)-N,N,2,3-Tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
(-)-N,N,2,3-Tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
2,3-Dimethyl-5-(morpholin-4-ylcarbonyl)-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene],

N-(2-Hydroxyethyl)-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
5-[(3,3-Difluoroazetidin-1-yl)carbonyl]-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene],
2,3-Dimethyl-5-(piperidin-1-ylcarbonyl)-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene],
N-Cyclopropyl-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
5-(Azetidin-1-ylcarbonyl)-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene],
5-(Aziridin-1-ylcarbonyl)-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene],
Methyl (3S)-3-{[(2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-inden]-5-yl)carbonyl]amino}-3-phenylpropanoate,
2,3-Dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
N-Methoxy-N,2,3-trimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
2,3-Dimethyl-5-(pyrrolidin-1-ylcarbonyl)-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene],
N,2,3-Trimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
N-(2-Methoxyethyl)-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
N-(2-Hydroxyethyl)-N,2,3-trimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
2,3-Dimethyl-5-(piperidin-1-ylcarbonyl)-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene],
(3S)-3-{[(2,3-Dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-inden]-5-yl)carbonyl]amino}-3-phenylpropanoic acid,
5'-Fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxylic acid,
N-Ethyl-5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
5'-Fluoro-N-methoxy-N,2,3-trimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
N-Cyclopropyl-5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
5'-Fluoro-5-[(3-methoxyazetidin-1-yl)carbonyl]-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene],

5'-Fluoro-2,3-dimethyl-N-(2,2,2-trifluoroethyl)-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide,
5-(Azetidin-1-ylcarbonyl)-5'-fluoro-2,3-dimethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene],
Ethyl 2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxylate,
N,N,2,3-tetramethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
2,3-Dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxylic acid,
N,2,3-Trimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
N-cyclopropyl-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
5-(Azetidin-1-ylcarbonyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene],
N-methoxy-N,2,3-trimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
N-isobutyl-N,2,3-trimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
N-cyclobutyl-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
N-(cyclopropylmethyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
N-ethyl-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
5-[(3-Methoxyazetidin-1-yl)carbonyl]-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene],
5-(Isoxazolidin-2-ylcarbonyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene],
2,3-Dimethyl-5-(1,2-oxazinan-2-ylcarbonyl)-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene],
N-(2-Hydroxyethyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
2,3-Dimethyl-N-(2,2,2-trifluoroethyl)-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
2,3-Dimethyl-5-(pyrrolidin-1-ylcarbonyl)-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene],
N-(2-Ethoxyethyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,

N-(3-Methoxypropyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
2,3-Dimethyl-N-[2-(methylthio)ethyl]-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
N-(2-Methoxyethyl)-2,3-dimethyl-1',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,2'-indene]-5-carboxamide,
Ethyl 2,3-dimethyl-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-h]quinoline-8,1'-indene]-5-carboxylate,
N,2,3-trimethyl-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-h]quinoline-8,1'-indene]-5-carboxamide and
N,N,2,3-tetramethyl-2',3,3',6,7,9-hexahydrospiro[imidazo[4,5-h]quinoline-8,1'-indene]-5-carboxamide
and its salts.

13. Use of a compound according to any of claims 1 to 12 for the production of medicaments which are employed for the treatment and/or prophylaxis of gastrointestinal disorders.

14. A medicament comprising one or more compounds according to any of claims 1 to 12 and/or a pharmaceutically acceptable salt thereof together with customary pharmaceutical excipients.

15. The use of a compound according to any of claims 1 to 12 and its pharmaceutically acceptable salts for the prevention and/or treatment of gastrointestinal disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/063886

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/10 C07D491/10 A61K31/438 A61K31/4188 A61P1/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/054984 A (ALTANA PHARMA AG [DE]; BUHR WILM [DE]; ZIMMERMANN PETER JAN [DE]) 1 July 2004 (2004-07-01) cited in the application abstract; claim 1	1-15
A	WO 2004/087701 A1 (ALTANA PHARMA AG [DE]; BUHR WILM [DE]; CHIESA M VITTORIA [DE]; ZIMMERM) 14 October 2004 (2004-10-14) cited in the application abstract; claim 1	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2008	01/04/2008

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/063886

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004054984 A	01-07-2004	AU 2003294831 A1	09-07-2004
		BR 0317041 A	25-10-2005
		CA 2508838 A1	01-07-2004
		HR 20050612 A2	31-08-2006
		IS 7926 A	01-07-2005
		JP 2006511600 T	06-04-2006
		KR 20050084170 A	26-08-2005
		MX PA05006052 A	18-08-2005
		US 2006194969 A1	31-08-2006
WO 2004087701 A1	14-10-2004	AU 2004226180 A1	14-10-2004
		BR PI0408893 A	11-04-2006
		CA 2520581 A1	14-10-2004
		CN 1764662 A	26-04-2006
		IS 8091 A	26-10-2005
		JP 2006522071 T	28-09-2006
		KR 20060015483 A	17-02-2006
		MX PA05010310 A	17-11-2005
		US 2006194968 A1	31-08-2006