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(54) **Eljárás 4-(benzimidazolil-metil-amino)-benzamidinek előállítására**

87701/03

METHOD FOR PRODUCING 4-(BENZIMIDAZOLYLMETHYLAMINO)-BENZAMIDINES

BACKGROUND TO THE INVENTION

1. TECHNICAL FIELD

The invention relates to a process for preparing an optionally substituted 4-(benzimidazol-2-ylmethylamino)-benzamidine, wherein

(a) an optionally suitably substituted diaminobenzene is condensed with 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-phenylamino]-acetic acid,

(b) the product thus obtained is hydrogenated, and

(c) optionally the amidino group is carbonylated.

2. PRIOR ART

Substituted (4-benzimidazol-2-ylmethylamino)-benzamidines, particularly 1-methyl-2-[*N*-[4-(*N*-n-hexyloxycarbonylamidino)phenyl]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-*N*-(2-pyridyl)-*N*-(2-ethoxycarbonylethyl)-amide, are already known from International Patent Application WO 98/37075 as active substances with a thrombin-inhibiting and thrombin time-prolonging activity.

The main field of indications for the compound of chemical formula I is the postoperative prevention of deep vein thrombosis.

In WO 98/37075 it is proposed to prepare the substituted (4-benzimidazol-2-ylmethylamino)-benzamidines by reacting the corresponding, substituted (4-benzimidazol-2-ylmethylamino)-benzonitriles with ammonia. This method is very onerous in terms of production costs and results in a high load of acids requiring disposal.

The aim of the present invention was to indicate an alternative method of preparing the substituted (4-benzimidazol-2-ylmethylamino)-benzamidines, by which this onerous stage of the production process could be avoided.

BRIEF SUMMARY OF THE INVENTION

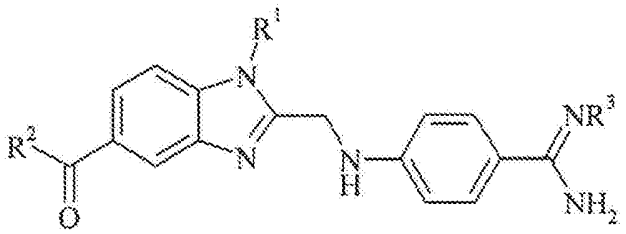
Surprisingly, it has now been found that substituted 4-(benzimidazol-2-ylmethylamino)-benzamidines can be prepared in high yields and using inexpensive adjuvants if

(a) an optionally suitably substituted diaminobenzene is condensed with 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-phenylamino]-acetic acid,

(b) the product thus obtained is hydrogenated, and

(c) optionally the amidino group is carbonylated, preferably with an alkylhalogen formate in the presence of a base, particularly with hexyl chloroformate.

The invention therefore relates to a process for preparing an optionally substituted 4-(benzimidazol-2-ylmethylamino)-benzamidine of formula (I)



(I)

wherein

R^1 denotes a methyl group,

R^2 denotes an $R^{21}NR^{22}$ group, wherein

R^{21} denotes an ethyl group which is substituted by an ethoxycarbonyl group,

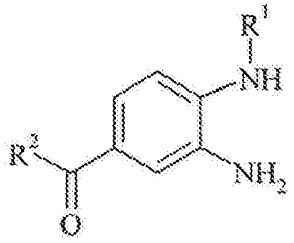
and

R^{22} denotes a pyridin-2-yl group,

and

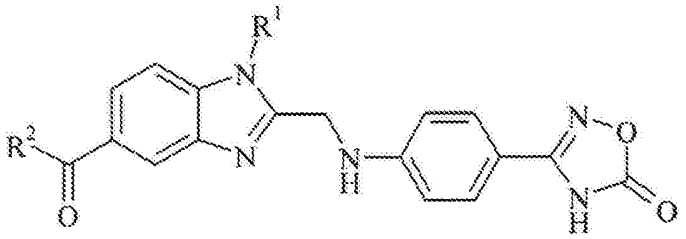
R^3 denotes a hexyloxycarbonyl group;

wherein in step (a) a phenyldiamine of formula (II)



(II)

wherein R^1 and R^2 have the meanings given for formula (I),
is reacted with 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-phenylamino]-acetic acid;
the resulting product of formula (III)



(III)

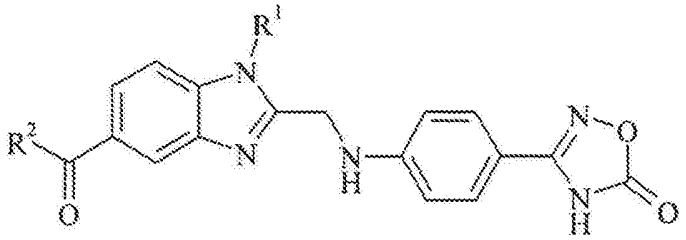
wherein R^1 and R^2 have the meanings given for formula (I),
is hydrogenated in step (b), and

(c) optionally the compound of formula (I) thus obtained wherein R^3 denotes hydrogen is reacted with a compound of formula (IV)

$$R^3\text{-}X \qquad (IV)$$

wherein R^3 has the meaning given for formula (I), and
X denotes a suitable leaving group.

The invention further relates to the new intermediate products of formula III involved in the process according to the invention:



(III)

wherein R^1 and R^2 have the meanings given for the subsequent compound of formula (I), and also 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-phenylamino]-acetic acid.

DETAILED DESCRIPTION OF THE INVENTION

Embodiments (A) to (D) of the process according to the invention are preferred:

(A) the condensation in step (a) is carried out in the presence of an inert diluent and a water-binding agent.

The correspondingly substituted diaminobenzenes of formula (II) are known, for example, from International Patent Application WO 98/37075 or may be prepared analogously to those described therein. It is particularly preferable to use 3-amino-4-methylaminobenzoic acid-*N*-(2-pyridyl)-*N*-(2-ethoxycarbonylethyl)-amide.

The inert diluents used may be both aprotic apolar solvents, such as e.g. aliphatic or aromatic, optionally halogenated hydrocarbons, or aprotic polar solvents such as e.g. ethers and/or amides or lactams and/or mixtures thereof. Aprotic apolar solvents used are preferably branched or unbranched $C_5 - C_8$ aliphatic alkanes, $C_4 - C_{10}$ cycloalkanes, $C_1 - C_8$ aliphatic haloalkanes, $C_6 - C_{10}$ aromatic alkanes or mixtures thereof. It is particularly preferable to use alkanes such as pentane, hexane or heptane, cycloalkanes such as cyclohexane or methylcyclohexane, haloalkanes such as dichloromethane, aromatic alkanes such as benzene, toluene or xylene or mixtures thereof. Suitable aprotic solvents are polar ethers such as for example tetrahydrofuran (THF), *tert*-butyl-methylether or dimethoxyethylether or amides such as for example dimethylformamide, or lactams such as for example N-methylpyrrolidone.

The water-binding agents used may be hygroscopic salts, inorganic or organic acids, anhydrides of inorganic or organic acids, molecular sieves or urea derivatives. 1,1´-Carbonyldiimidazole is particularly preferred.

In a particularly preferred embodiment 1,1´-carbonyldiimidazole is suspended in THF and heated. 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-phenylamino]-acetic acid is added. The correspondingly substituted diaminobenzene is added in THF. The reaction mixture is stirred at about 50°C and then after the addition of ethyl acetate it is concentrated by evaporation.

(B) The hydrogenation in step (b) is carried out in the presence of an inert diluent and a hydrogenation catalyst.

In a particularly preferred process, the hydrogenation is carried out in a temperature range from 0°C to 100°C, preferably from 0°C to 50°C, particularly from 10°C to 30°C.

Also preferred is a process wherein the hydrogenation is carried out under a pressure of more than 0.5 bar to 100 bar, preferably under a pressure of 1 bar to 10 bar, particularly at about 1 - 2 bar.

The inert diluents used may be both protic solvents - such as e.g. alcohols, carboxylic acids and/or water - or aprotic polar solvents such as e.g. ethers and/or amides or lactams and/or mixtures thereof. Water may optionally be added to all the solvents. Preferred protic solvents used are branched or unbranched C_1 – C_8 alkanols, C_1 – C_3 carboxylic acids or mixtures thereof. Particularly preferably, lower alcohols such as methanol, ethanol, n-propanol and isopropanol, carboxylic acids such as formic acid, acetic acid and propionic acid or mixtures thereof are used. The particularly preferred reaction medium is ethanol and/or acetic acid, which may optionally contain water. Suitable aprotic solvents are polar ethers such as for example tetrahydrofuran or dimethoxyethylether or amides such as for example dimethylformamide, or lactams such as for example N-methylpyrrolidone. It is preferable to use solvents with a low tendency to flammability.

Suitable hydrogenation catalysts are generally transition metals such as for example nickel, platinum or palladium or the salts or oxides thereof. Raney

nickel, platinum oxide and palladium on an inert carrier material, particularly palladium on activated charcoal (Pd/C), are preferred.

Preferred processes are those wherein during the hydrogenation the product of step (a) is used in a ratio by weight of from 1:1 to 1000:1, preferably from 5:1 to 100:1 to the hydrogenation catalyst.

In a particularly preferred embodiment the product of step (a) is taken up in ethanol and after the addition of acetic acid hydrogenated with water-dampened 10% Pd/C at ambient temperature and at 2 bar hydrogen. The catalyst is filtered off and p-toluenesulphonic acid dissolved in 90 ml of ethanol is added to the filtrate. The tosylate of the 4-(benzimidazol-2-ylmethylamino)-benzamidine obtained is precipitated out, filtered off and washed with ethanol in several batches.

(C) In order to prepare 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-phenylamino]-acetic acid, 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-aniline is reacted with a 2-haloacetic acid ester, preferably ethyl bromoacetate, in the presence of a weak base, preferably a tertiary amine, such as for example triethylamine or an alkali metal carbonate, such as for example sodium carbonate in an inert solvent, and the 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-phenylamino]-acetic acid ester obtained is saponified.

The inert diluents used may be either protic solvents - such as e.g. alcohols, and/or water - or aprotic polar solvents such as e.g. ethers and/or amides or lactams and/or mixtures thereof. Water may optionally be added to all the solvents. Preferably, branched or unbranched $C_1 - C_8$ alkanols or mixtures thereof are used as protic solvents. Particularly preferably, lower alcohols such as methanol, ethanol, n-propanol and isopropanol or mixtures thereof are used. The particularly preferred reaction medium is isopropanol, which may optionally contain water. Suitable aprotic solvents are polar ethers such as for example tetrahydrofuran or dimethoxyethylether or amides such as for example dimethylformamide, or lactams such as for example N-methylpyrrolidone.

In a particularly preferred embodiment, ethyl bromoacetate is metered into a suspension of 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-aniline and sodium carbonate in water/isopropanol and stirred. The cooled suspension is suction filtered, washed with water and ethanol in several batches and dried.

The saponification is preferably carried out in a protic solvent with an alkali metal or alkaline earth metal hydroxide, particularly with lithium, sodium or potassium hydroxide.

In a particularly preferred embodiment, 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-phenylamino]-acetic acid ester is suspended in water and an aqueous solution of NaOH is slowly added at ambient temperature. The suspension changes into a solution and is heated to 45 to 75°C. HCl is added to the solution thus obtained until a pH of about 5 is achieved. The solid is isolated and washed with cold water and cold ethanol and MtBE.

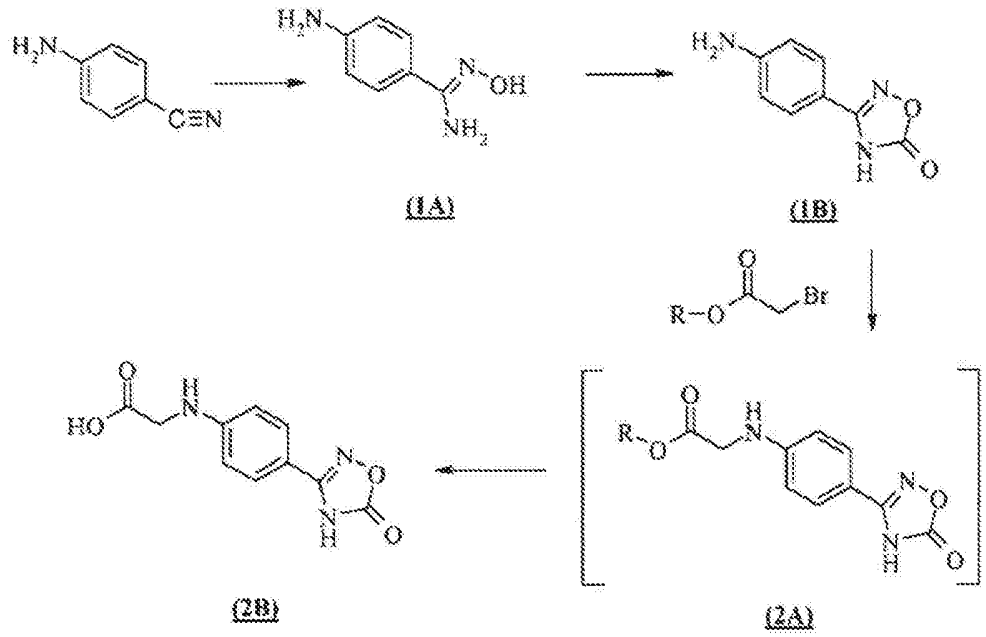
(D) In order to prepare 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-aniline, 4-aminophenyl-amidoxime is reacted with a dialkylcarbonate, preferably dimethylcarbonate or diethyl carbonate in the presence of a base, preferably an alkali metal alkoxide, particularly sodium methoxide, sodium ethoxide or potassium *tert*-butoxide.

4-Aminophenyl-amidoxime may be prepared for example by reacting 4-aminobenzonitrile with hydroxylamine hydrochloride.

In a particularly preferred embodiment, sodium methoxide is added at 70 – 75°C to a suspension of 4-aminophenyl-amidoxime in ethanol and rinsed with ethanol. After 15 min stirring, diethylcarbonate is added dropwise. After 2-4 hours' reaction the mixture is cooled and ethanol is distilled off at 120 mbar and 40°C. The residue is taken up in water and after heating adjusted to pH 10-12 with semi-conc. sodium hydroxide solution, then adjusted to pH 5-6 by acidification with conc. hydrochloric acid and slowly cooled. The solution changes into a suspension, which is filtered and washed several times with cold water and ethanol.

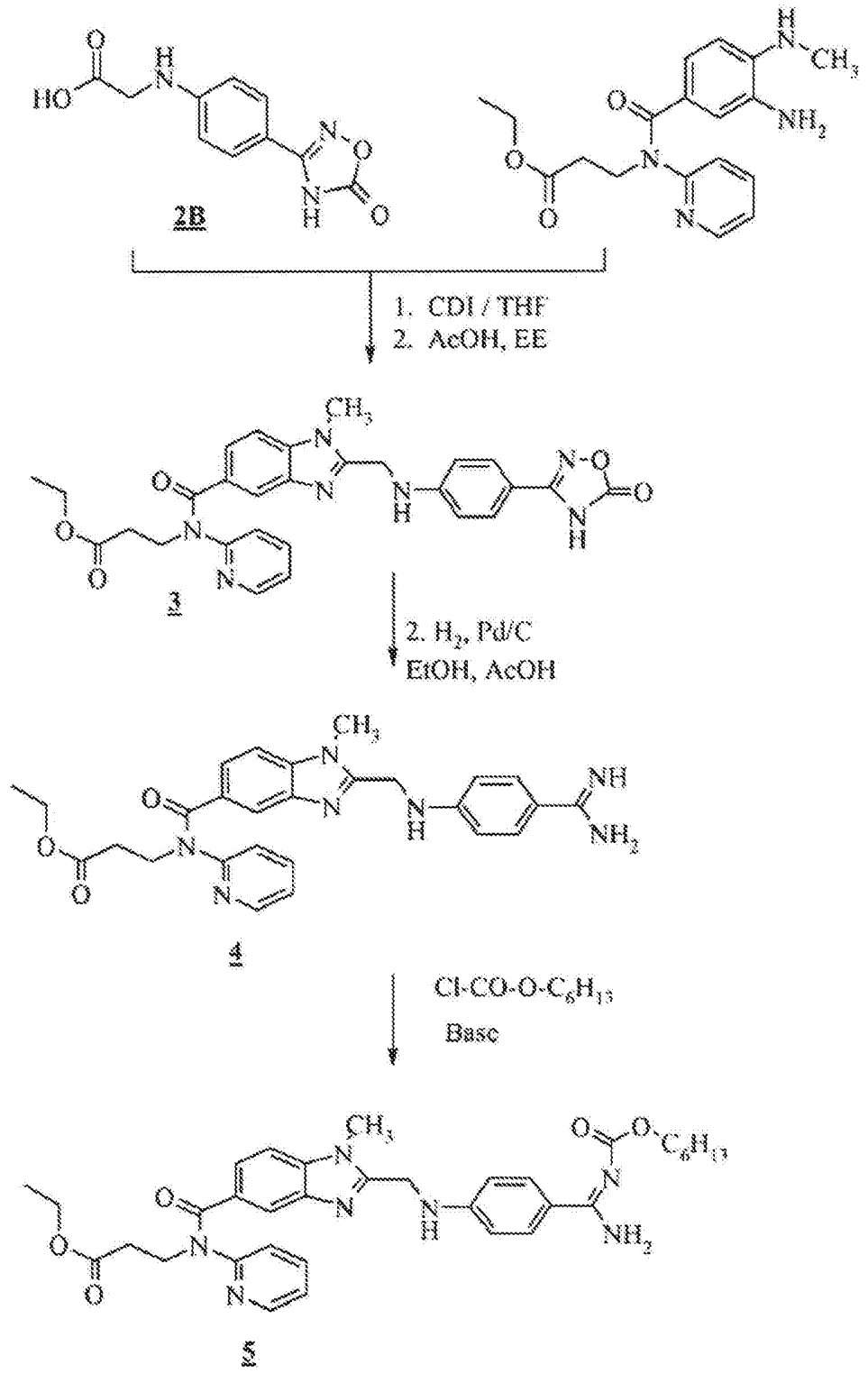
The preparation of the 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-phenylamino]-acetic acid required as an intermediate product from 4-aminobenzonitrile is illustrated in the reaction scheme shown below:

Scheme I



The preparation of a 4-(benzimidazol-2-ylmethylamino)-benzamidine is illustrated by way of example in the following reaction scheme:

Scheme II



The working up of the individual reactions may be carried out in the conventional manner, e.g. by separating off the reaction adjuvants, eliminating the solvent and isolating the pure end product from the residue by crystallisation, distillation, extraction or chromatography.

The process according to the invention will now be illustrated by means of the Examples that follow. The skilled man will be aware that the Examples serve purely as an illustration and are not to be viewed in a limiting capacity.

Examples

The following abbreviations are used hereinbefore and hereinafter:

AcOH	acetic acid
AMBPA	3-amino-4-methylaminobenzoic acid-*N*-(2-pyridyl)-*N*-(2-ethoxycarbonylethyl)-amide
CDI	1,1´-carbonyldiimidazole
EE	ethyl acetate
EtOH	ethanol
HCl	hydrochloric acid
MtBE	methyl-*tert*-butyl ether
NaOH	sodium hydroxide
PTSA	p-toluenesulphonic acid
RT	ambient temperature
THF	tetrahydrofuran

Example 1 - Preparation of 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-aniline (1):

(1A) - In the reaction vessel 118.6 g (1 mol) 4-aminobenzonitrile and 68.9 g (0.65 mol) sodium carbonate are placed in 500 ml of ethanol and 100 ml of water and heated to 60°C. 76.4 g (1.1 mol) hydroxylamine hydrochloride, dissolved in 100 ml of water, are slowly added dropwise to this suspension.

The mixture is then stirred overnight at 60°C. On cooling to 0-5°C the substance is precipitated out, filtered off and washed several times with a total of 150 ml cold water and 100 ml cold ethanol. Finally, it is washed with 50 ml MtBE and 178.4 g of damp product is obtained. This is dried *in vacuo* at 35°C.

Yield: 135.4 g light beige substance (89.5% of theoretical),
melting point: from 169.5°C (decomp.);
purity: > 98% HPLC peak area

(1B) - 25.02 g (0.46 mol) sodium methoxide are added batchwise to a suspension of 60.5 g (1A) (0.4 mol) in 400 ml of ethanol at 70-75°C and rinsed with 20 ml of ethanol.

After 15 min stirring 47.25 g (0.4 mol) diethylcarbonate are added dropwise. After 3 hours' reaction the mixture is cooled to 40°C and the ethanol is distilled off at 120 mbar and 40°C. A dark residue is obtained. This is dissolved in 350 ml of water at 40-45°C and after heating to 70°C first adjusted to pH 11 by the slow addition of semi-conc. sodium hydroxide solution; then adjusted to pH 5.5 by acidification with conc. hydrochloric acid and slowly cooled. The solution changes into a suspension which is filtered and washed several times with a total of 150 ml cold water and 50 ml of ethanol.

88.7 g of damp substance are obtained, which is dried at 35°C *in vacuo*.
Yield: 62 g dark substance (87.5% of theory);
melting point: from 178°C (decomp.);
purity: > 98% HPLC peak area

Example 2 - Preparation of 2-[4-(1,2,4-oxadiazol-5-on-3-yl)-phenylamino]-acetic acid (2):

(2A) - At ambient temperature 83.5 g (0.5 mol) ethyl bromoacetate are metered into a suspension of 70.86 g (0.4 mol) (1B) and 26.5 g (0.25 mol) sodium carbonate in 600 ml of water/isopropanol and stirred overnight. The reaction mixture turns reddish-brown to orange.

The suspension cooled to 0°C is suction filtered, washed in several batches with 300 ml of water and 150 ml of ethanol (106 g damp light-brown substance) and dried *in vacuo* at 35°C.

Yield: 92.44 g brownish substance (87.7% of theory)
Melting point: from 186.1°C (decomp.)
Purity: > 98% HPLC peak area

(2B) - The ester (2A) thus obtained (86.9 g; 0.33 mol) is suspended in 400 ml of water and at RT 120 g of 45% NaOH are slowly added dropwise. The suspension goes into solution and turns reddish (pH 12.5). It is heated to ~60°C and saponified for 1 h . The solution obtained is combined batchwise with 37% HCl until a pH of 5 is achieved. The mixture is cooled to 0°C. The solid is suction filtered and washed in several batches with a total of 400 ml cold water as well as 40 ml each of cold ethanol and MtBE. 81.4 g damp dark substance is obtained. It is dried *in vacuo* at 35°C.

Yield: 76.7 g substance (98% of theory)
Melting point: from 193°C (decomp.)
Purity: > 99% HPLC peak area

Example 3 - Preparation of 1-methyl-2-[*N*-[4-(1,2,4-oxadiazol-5-on-3-yl)phenyl]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-*N*-(2-pyridyl)-*N*-(2-ethoxycarbonylethyl)-amide (3):

11.35 g (70 mmol) 1,1´-carbonyldiimidazole are suspended in 100 ml THF and heated to 50°C. 14.23 g (60.5 mmol) (2B) are added batchwise. 17.1 g (50 mmol) AMPBA are dissolved in 37 ml THF with heating to 50°C.

After approx. 90 min the suspension is metered into the solution of AMPBA and rinsed with 20 ml THF. The reaction mixture is stirred for approx. 18 h and then refluxed after the addition of 100 ml acetic acid, so that the THF is distilled off. After approx. 1 h, 400 ml of water are added and the mixture is stirred.

The solution is cooled, the pink solid substance precipitated is filtered off and washed in 2 batches with 20 ml of water and dried *in vacuo* at max 50°C. The isolated substance is the diacetate of **(3)**.

Yield: 24.8 g substance (75% of theory);
melting point: from 167°C with decomp. (DSC);
purity: > 95% HPLC peak area

Example 4 - Preparation of 1-methyl-2-[*N*-[4-amidinophenyl]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-*N*-(2-pyridyl)-*N*-(2-ethoxycarbonylethyl)-amide (4)

37.3 g (56.4 mmol) (3) are dissolved in 900 ml of ethanol and, after the addition of 10 ml acetic acid, hydrogenated with 4 g of water-dampened 10% Pd/C at RT and at 2 bar hydrogen. The catalyst is filtered off and 17 g (89.4 mmol) PTSA, dissolved in 180 ml of ethanol, are added to the filtrate. The tosylate of (4) is precipitated out, filtered off and washed again with 150 ml of ethanol in several batches. Damp substance is obtained which is dried *in vacuo* at 35°C.

Yield: 34.5 g light beige substance (91.3% of theory);
melting point: 187°C (DSC);

purity: > 98% HPLC peak area.

Example 5 - Preparation of 1-methyl-2-[*N*-[4-(*N*-n-hexyloxycarbonylamidino)phenyl]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-*N*-(2-pyridyl)-*N*-(2-ethoxycarbonylethyl)-amide (5)

The compound obtained according to Example 4 is reacted with hexyl chloroformate in known manner in the presence of a base.

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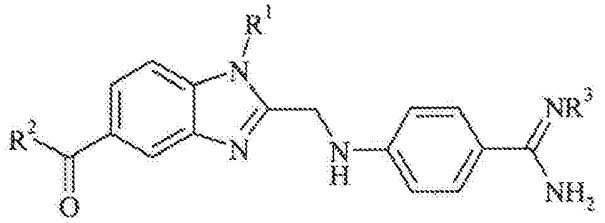
Eljárás 4-(benzimidazolil-metil-amino)-benzamidinek előállítására

Szabadalmi igénypontok

1. Eljárás az (I) általános képletű, adott esetben szubsztituált (4-benzimidazol-2-il-metil-amino)-benzamidin előállítására



(I)

ahol

R^1 jelentése metilcsoport,

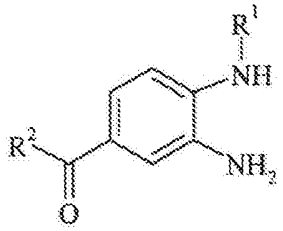
R^2 jelentése egy $R^{21}NR^{22}$ csoport, ahol

R^{21} jelentése etilcsoport, amely etoxi-karbonil-csoporttal van szubsztituálva, és

R^{22} jelentése piridin-2-il-csoport és

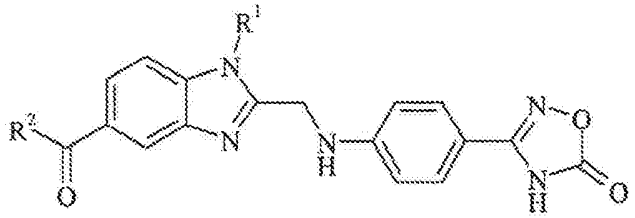
R^3 jelentése hexiloxi-karbonil-csoport,

ahol az (a) lépésben egy (II) általános képletű fenil-diamint



(II)

ahol R^1 és R^2 jelentése az (I) általános képletnél megadott, 2-[4-(1,2,4-oxadiazol-5-on-3-il)-fenil-amino]-ecetsavval reagáltatunk, a kapott (III) általános képletű terméket



(III)

ahol R^1 és R^2 jelentése az (I) általános képletnél megadott, a (b) lépésben hidrogénezzük és

(c) a kapott (I) általános képletű vegyületet, ahol R^3 jelentése hidrogén, adott esetben egy (IV) általános képletű vegyülettel reagáltatjuk

$$R^3\text{-}X \qquad (IV)$$

ahol R^3 jelentése az (I) általános képletnél megadott és X jelentése alkalmas kilépő csoport.

2. Az előző igénypontok egyike szerinti eljárás, **azzal jellemezve, hogy** az (a) lépésben a kondenzációt közömbös hígítószer és vízmegkötőszer jelenlétében folytatjuk le.

3. Az előző igénypontok egyike szerinti eljárás, **azzal jellemezve, hogy** a (b) lépésben a hidrogénezést közömbös hígítószer és hidrogénező katalizátor jelenlétében végezzük ki.

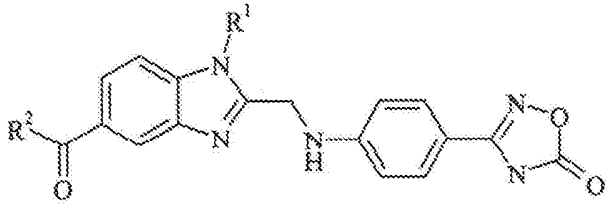
4. Az előző igénypontok egyike szerinti eljárás, **azzal jellemezve, hogy** a 2-[4-(1,2,4-oxadiazol-5-on-3-il)-fenil-amino]-ecetsav előállítására 2-[4-(1,2,4-oxadiazol-5-on-3-il)]-anilint 2-halogén-ecetsav-észterrel reagáltatunk gyenge bázis jelenlétében, és a kapott 2-[4-(1,2,4-oxadiazol-5-on-3-il)-fenil-amino]-ecetsav-észtert elszappanosítjuk.

5. Az előző igénypontok egyike szerinti eljárás, **azzal jellemezve, hogy** a 2-[4-(1,2,4-oxadiazol-5-on-3-il)]-anilin előállítására 4-amino-fenil-amidoximot dialkil-karbonáttal reagáltatunk bázis jelenlétében.

6. Az előző igénypontok egyike szerinti eljárás, **azzal jellemezve, hogy** a kapott (I) általános képletű vegyületet fiziológiailag elfogadható sóvá alakítjuk.

7. A 6. igénypont szerinti eljárás, **azzal jellemezve, hogy** a fiziológiailag elfogadható só metán-szulfonát.

8. A (III) általános képletű vegyület



(III)

ahol R^1 és R^2 jelentése az (I) általános képletnél megadott.

9. 2-[4-(1,2,4-oxadiazol-5-on-3-il)-fenil-amino]-ecetsav.