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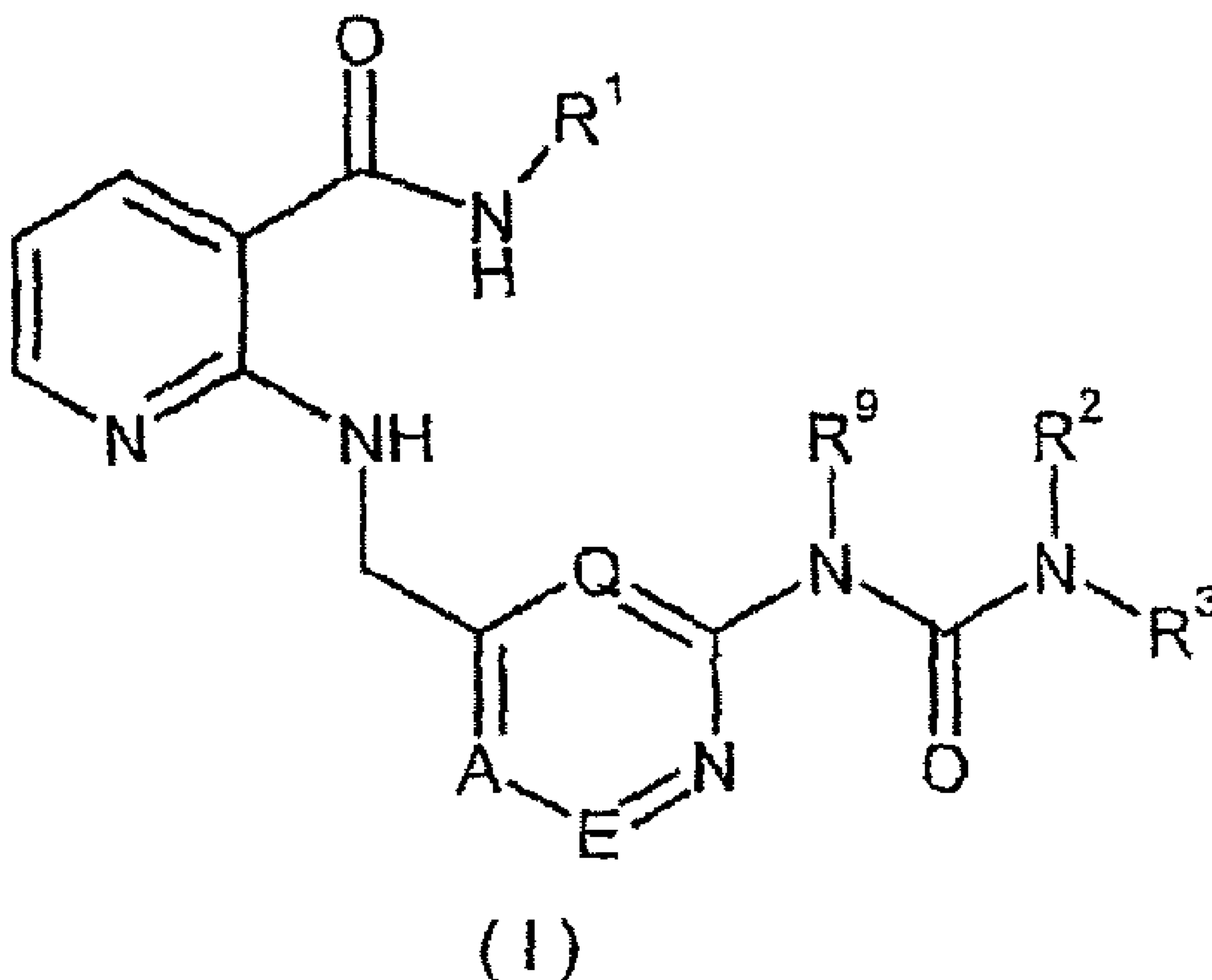
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(54) Titre : NICOTINAMIDE PYRIDINUREAS UTILES COMME INHIBITEURS DE KINASE DANS LE RECEPTEUR DU
 FACTEUR DE CROISSANCE DE L'ENDOTHELIUM VASCULAIRE (VEGF)
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 KINASE INHIBITORS



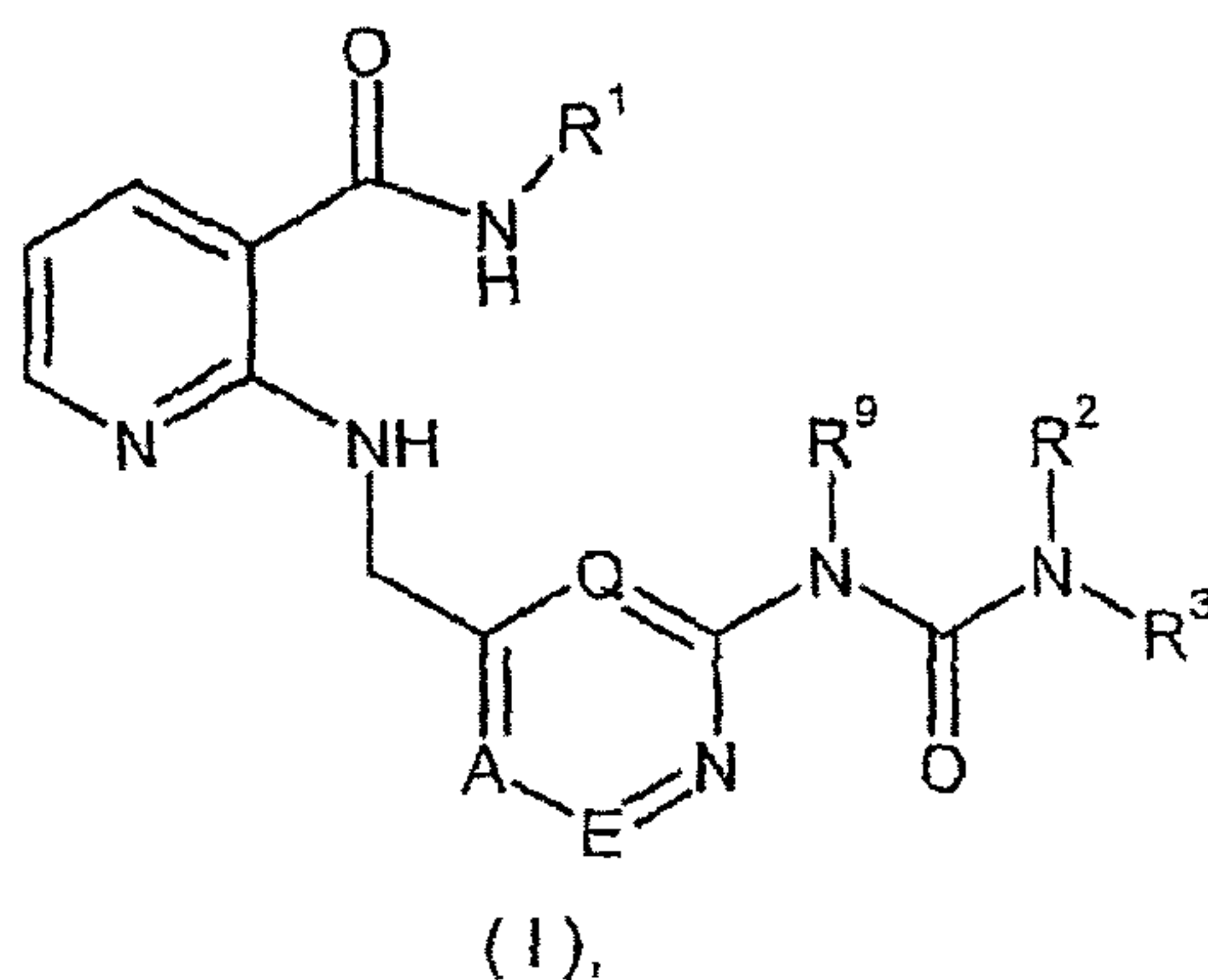
(57) Abrégé/Abstract:

The invention relates to novel nicotinamide pyridinureas as VEGF receptor kinase inhibitors, their production and use as pharmaceutical agents for preventing or treating diseases that are triggered by persistent angiogenesis. In one aspect of the invention, the nicotinamide pyridinureas are compounds of the general formula (I): (see formula I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof.



ABSTRACT

The invention relates to novel nicotinamide pyridinureas as VEGF receptor kinase inhibitors, their production and use as pharmaceutical agents for preventing or treating diseases that are triggered by persistent angiogenesis. In one aspect of the invention, the nicotinamide pyridinureas are compounds of the general formula (I):



or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof.

Nicotinamide Pyridinureas as Vascular Endothelial Growth Factor (VEGF) Receptor Kinase Inhibitors

The invention relates to novel anthranilamide pyridinureas as VEGF receptor
5 kinase inhibitors, their production and use as pharmaceutical agents for
preventing or treating diseases that are triggered by persistent angiogenesis.

Many diseases are known to be associated with persistent angiogenesis, for
example, diseases such as tumor- or metastases-growth; psoriasis; arthritis,
10 such as rheumatoid arthritis, hemangioma, endometriosis, angiofibroma; eye
diseases, such as diabetic retinopathy, neovascular glaucoma; renal diseases,
such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis,
thrombotic microangiopathic syndrome, transplant rejections and
glomerulopathy; fibrotic diseases, such as cirrhosis of the liver, mesangial cell
15 proliferative diseases and arteriosclerosis.

Lymphangiogenesis is a process accompanying tumor growth and metastases.
It is prominent in lymphedema, lymphangiectasia, lymphangioma, and
lymphangiosarcoma and in asthmatic disease, where lymph vessels are
20 chronically overexpressed in the lung.

Persistent angiogenesis is induced by the factor VEGF via its receptors. In
order for VEGF to exert this action, it is necessary that VEGF bind to the
receptor, and that a tyrosine phosphorylation is induced.

25

Direct or indirect inhibition of the VEGF receptor can be used for preventing
or treating such diseases and other VEGF-induced pathological angiogenesis
and vascular permeable conditions, such as tumor vascularization. For
example, it is known that the growth of tumors can be inhibited by soluble
30 receptors and antibodies against VEGF, an example for the latter being

Avastin[®] whose treatment paradigm has been introduced in human cancer therapy.

Anthranilic acid amides effective in the treatment of psoriasis; arthritis, such
5 as rheumatoid arthritis, hemangioma, angiofibroma; eye diseases, such as
diabetic retinopathy, neovascular glaucoma; renal diseases, such as
glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis,
thrombic microangiopathic syndrome, transplant rejections and
glomerulopathy; fibrotic diseases, such as cirrhosis of the liver, mesangial cell
10 proliferative diseases, arteriosclerosis, injuries to nerve tissue, and for
inhibiting the reocclusion of vessels after balloon catheter treatment, in
vascular prosthetics or after mechanical devices are used to keep vessels open,
such as, e.g., stents, have been reported in WO 00/27820.

15 Anthranilic acid amides that are effective in the treatment of tumor or
metastasis growth, psoriasis, Kaposi's sarcoma, restenosis, such as, e.g., stent-
induced restenosis, endometriosis, Crohn's disease, Hodgkin's disease,
leukemia; arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma;
eye diseases, such as diabetic retinopathy, neovascular glaucoma; renal
20 diseases, such as glomerulonephritis, diabetic nephropathy, malignant
nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections
and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver, mesangial
cell proliferative diseases, arteriosclerosis, injuries to nerve tissue, and for
inhibiting the reocclusion of vessels after balloon catheter treatment, in
25 vascular prosthetics or after mechanical devices are used to keep vessels open,
such as, e.g., stents, as immunosuppressive agents, as a support in scar-free
healing, in senile keratosis and in contact dermatitis have also been reported in
WO 04/13102.

30 There is, however, a desire to produce compounds that are as efficacious as
possible in as broad a range of indications as possible. A constant blockade of

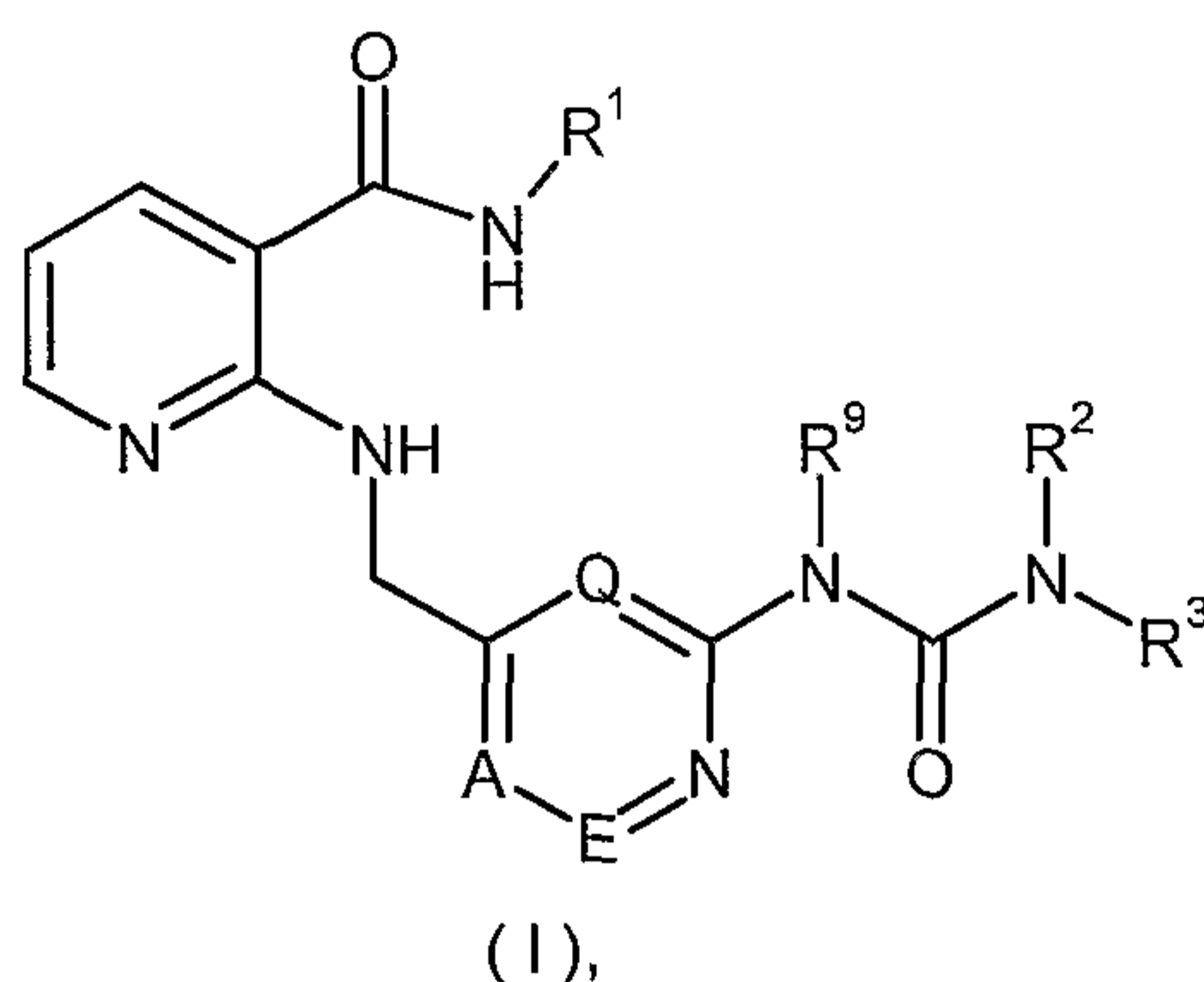
VEGF mediated signal transduction is desirable in order to reduce persistent angiogenesis and lymphangiogenesis. Suitable compounds for longer term treatment should exhibit little or no drug-drug interaction potential. The Cytochrome P450 isoenzymes play a pivotal role in the degradation of pharmaceutical agents. The problem is also complicated by the fact that patients may express different relative amounts of the isoenzymes. An inhibition of these isoenzymes may result in undesirable pharmaceutical agent interactions, especially in the case of multimorbid patients (patients with multiple disease conditions). For example, inhibition of the Cytochrome P450 isoenzymes responsible for metabolism of the parent agent could lead to toxic systemic concentrations. A further problem exists in combination therapy with other medications, whereby inhibition of the Cytochrome P450 isoenzymes responsible for metabolising the co-medications could lead to toxic systemic concentrations of the co-medication. This is especially the case for co-administered cytostatics in the case of cancer therapy.

Thus, it has now surprisingly been found that compounds of general formula (I), as described below, have more advantageous physico-chemical and/or pharmacokinetic properties and prevent, for example, tyrosine phosphorylation or stop persistent angiogenesis and thus the growth and propagation of tumors, whereby they are distinguished in particular by a potent inhibition of VEGF receptor kinases and a reduced potential for drug-drug interactions, specifically a reduced inhibition of cytochrome P450 isoenzymes 2C9 and 2C19.

25

The compounds of formula (I) are thus suitable, for example, for the treatment or prevention of diseases for which an inhibition of angiogenesis and/or the VEGF receptor kinases is beneficial.

30 In one aspect of the invention, there is provide a nicotinamide pyridinurea compound of formula (I) :



wherein:

5 A, E and Q independently of one another, are CH or N, whereby only a maximum of two nitrogen atoms are contained in the ring; preferably A, E, and Q are each CH;

10 R^1 is aryl or heteroaryl, which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C_1 - C_{12} -alkyl, C_3 - C_6 -cycloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, aralkyloxy, C_1 - C_{12} -alkoxy, halo- C_1 - C_6 -alkyl, cyano- C_1 - C_6 -alkyl, =O, $-SO_2R^6$, $-OR^5$, $-SOR^4$, $-COR^6$, $-CO_2R^6$ or $-NR^7R^8$, whereby C_1 - C_{12} -alkyl may be substituted with $-OR^5$ or $-NR^7R^8$; preferably phenyl, isoquinolyl, quinolynyl or indazolyl optionally substituted

15 in one or more places in the same way or differently with halogen, hydroxy, C_1 - C_{12} -alkyl, C_3 - C_6 -cycloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, aralkyloxy, C_1 - C_{12} -alkoxy, halo- C_1 - C_6 -alkyl, cyano- C_1 - C_6 -alkyl, =O, $-SO_2R^6$, $-OR^5$, $-SOR^4$, $-COR^6$, $-CO_2R^6$ or $-NR^7R^8$, whereby C_1 - C_{12} -alkyl may be substituted with $-OR^5$ or $-NR^7R^8$;

20 more preferably indazolyl substituted in one or more places in the same way or differently with halogen, hydroxy, C_1 - C_{12} -alkyl, C_3 - C_6 -cycloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, aralkyloxy, C_1 - C_{12} -alkoxy, halo- C_1 - C_6 -alkyl, cyano- C_1 - C_6 -alkyl, =O, $-SO_2R^6$, $-OR^5$, $-SOR^4$, $-COR^6$, $-CO_2R^6$ or $-NR^7R^8$, whereby C_1 - C_{12} -alkyl may be

25 substituted with $-OR^5$ or $-NR^7R^8$; even more preferably indazolyl

substituted with C₁-C₁₂-alkyl; more preferably indazolyl substituted with -CH₃, particularly 2-methyl-indazolyl;

R², R³ and R⁹ independently of one another, are hydrogen or C₁-C₁₂ alkyl optionally substituted with halogen, -OR⁵, or C₁-C₁₂-alkoxy; preferably hydrogen or unsubstituted C₁-C₁₂ alkyl; more preferably hydrogen or -CH₃; or

R⁹ is hydrogen, and

R² and R³ together with the nitrogen atom to which they are attached form a 3-8 membered heterocycloalkyl ring, preferably a 4-7 membered heterocycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulphur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶, or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵; preferably R² and R³ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl ring, which contains no or at least one further heteroatom, such as nitrogen, oxygen or sulphur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶, or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵; or

R³ is hydrogen or C₁-C₁₂-alkyl, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵; preferably is hydrogen or -CH₃; more particularly preferred hydrogen, and

R² and R⁹ together with the two nitrogen atoms to which they are attached form a 5-7 membered ring, preferably a 5 or 6 membered ring, which may be optionally further substituted in one or more places in the same way or differently with halogen, C₁-C₁₂-alkyl,

C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, or =O, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵; preferably together with the two nitrogen atoms to which they are attached form a 5-7 membered saturated ring, preferably a 5 or 6 membered saturated ring, which may be optionally further substituted in one or more places in the same way or differently with halogen, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, or =O, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵; more preferably together with the two nitrogen atoms to which they are attached form a 5 membered saturated ring, optionally further substituted in one or more places in the same way or differently with halogen, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, or =O, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

15 R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl; preferably C₁-C₁₂-alkyl; more preferably -CH₃;

R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl; preferably -CH₃ or hydrogen; more preferably hydrogen;

20 R⁶ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl, or -NR⁷R⁸; preferably C₁-C₁₂-alkyl or -NR⁷R⁸; more preferably -CH₃;

R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl, or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, preferably a 4-7 membered cycloalkyl ring, more preferably a 5 or 6 membered ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulphur, and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵,

30

COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶; preferably R⁷ and R⁸ independently of one another, are hydrogen, COR⁶, -SO₂R⁶, C₁-C₁₂-alkyl; more preferably hydrogen or C₁-C₁₂-alkyl; more preferably hydrogen or -CH₃,

5 and as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

In a second aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an
10 isomer, diastereoisomer, enantiomer, tautomer or salt thereof.

In a third aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof and at least one
15 pharmaceutically acceptable carrier, diluent or excipient.

In a fourth aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use in the
20 prevention or treatment of diseases associated with persistent angiogenesis and/or diseases associated with excessive lymphangiogenesis.

In a fifth aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use in the prevention
25 or treatment of tumor- or metastases-growth; psoriasis; Kaposi's sarcoma; restenosis including stent-induced restenosis; Crohn's disease; Hodgkin's disease; leukemia; arthritis including rheumatoid arthritis, hemangioma, angiofibroma; endometriosis; eye diseases including diabetic retinopathy,
30 neovascular glaucoma; corneal transplants; renal diseases, including glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis,

thrombotic microangiopathic syndrome, transplant rejections and glomerulopathy; fibrotic diseases, including cirrhosis of the liver; mesangial cell proliferative diseases; arteriosclerosis; injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment; in 5 vascular prosthetics or after mechanical devices are used to keep vessels open, as immunosuppressive agent for supporting scar-free healing; senile keratosis; contact dermatitis; and asthma.

In a sixth aspect of the present invention, there is provided a pharmaceutical 10 agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use as VEGF receptor kinase 3-inhibitors of lymphangiogenesis.

In a seventh aspect of the present invention, there is provided a pharmaceutical 15 agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use in a method for the treatment of the human or animal body.

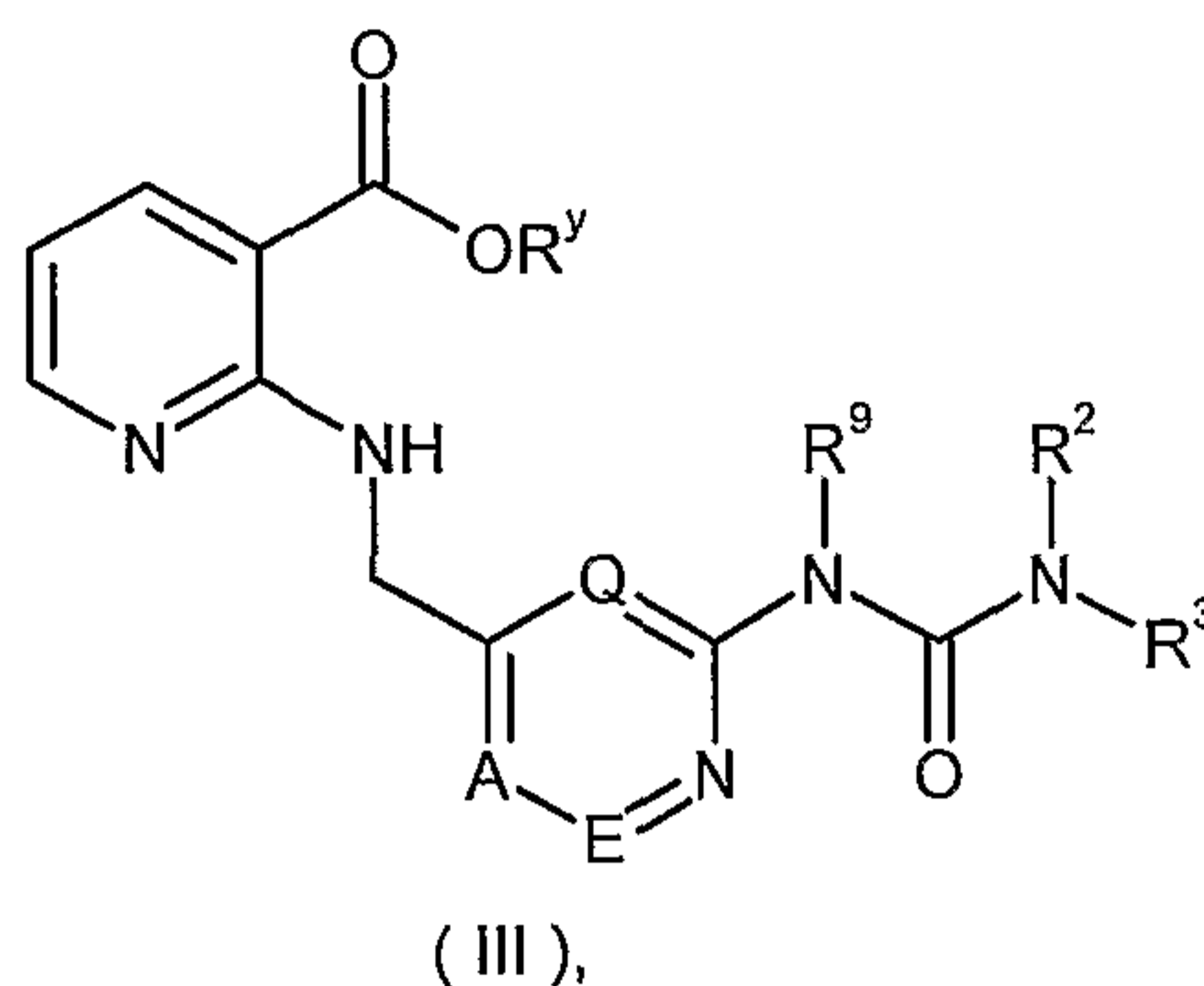
In a eighth aspect of the present invention, there is provided a pharmaceutical 20 agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use in the preparation of a pharmaceutical product for the treatment of a disease for which an inhibition of angiogenesis and/or lymphangiogenesis and/or the VEGF receptor kinases is beneficial.

25

In a ninth aspect of the present invention, there is provided a pharmaceutical 30 agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use as an inhibitor of the tyrosine kinases VEGFR-1 and VEGFR-2.

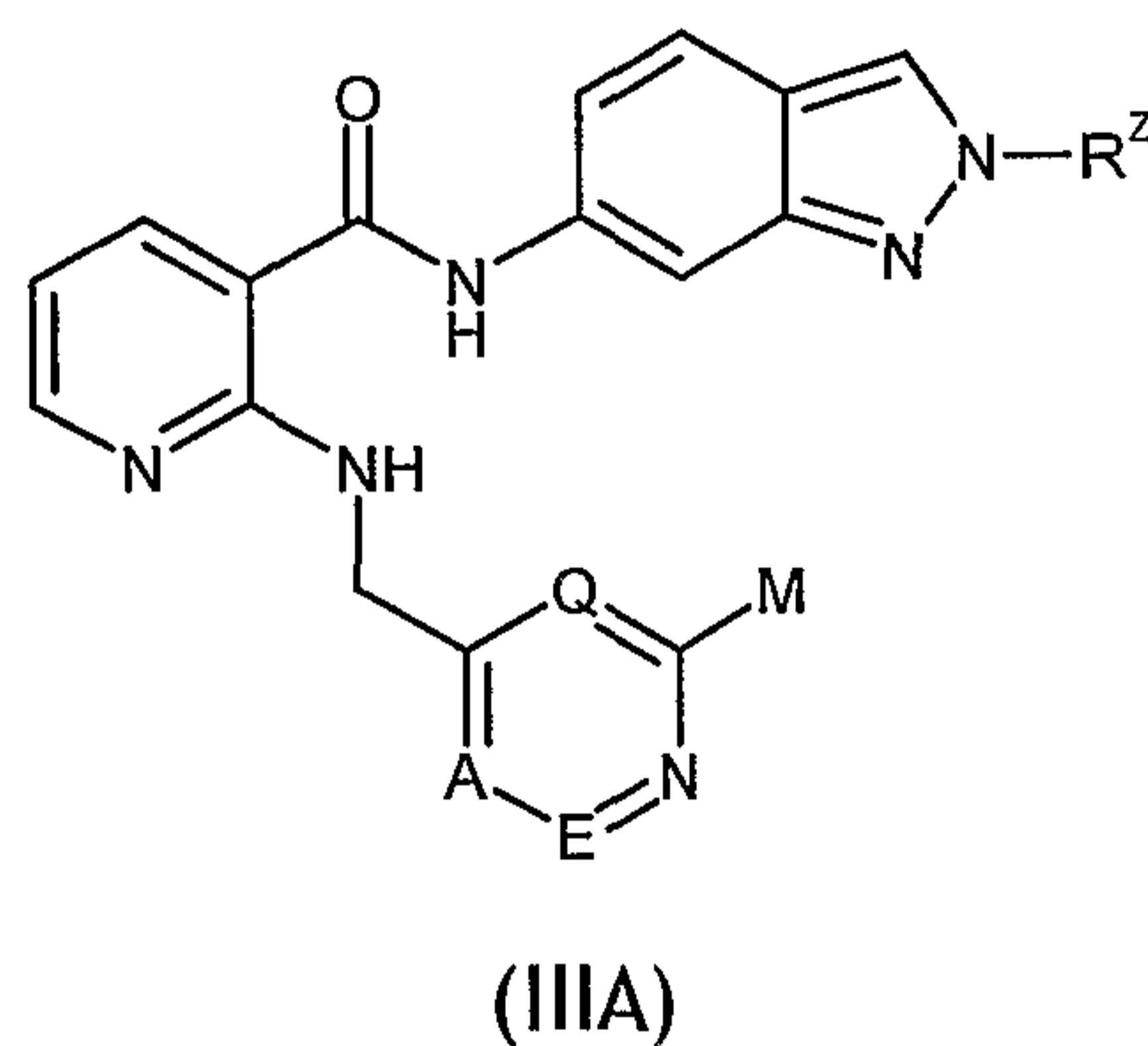
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In a tenth aspect of the present invention, there is provided a compound of general formula (III) :



5 in which A, E, Q, R², R³ and R⁹, are as defined for formula (I) *supra* and R^y is H or C₁-C₆-alkyl, as an intermediate for the preparation of a compound of formula (I) as defined *supra*. Preferably R^y is H or C₁-C₂-alkyl; more preferably R^y is H or -CH₃.

10 In an eleventh aspect of the present invention, there is provided a compound of general formula (IIIA) :



15

in which A, E, Q, W and are as defined for formula (I) *supra*, R^Z is C₁-C₁₂-alkyl and M is halogen, as an intermediate for the preparation of a compound of formula (I) as defined *supra*. Preferably, M = a chlorine atom.

20 In a twelfth aspect of the present invention, there is provided the use of a compound of general formula (III), in which A, E, Q, R², R³ and R⁹ are as

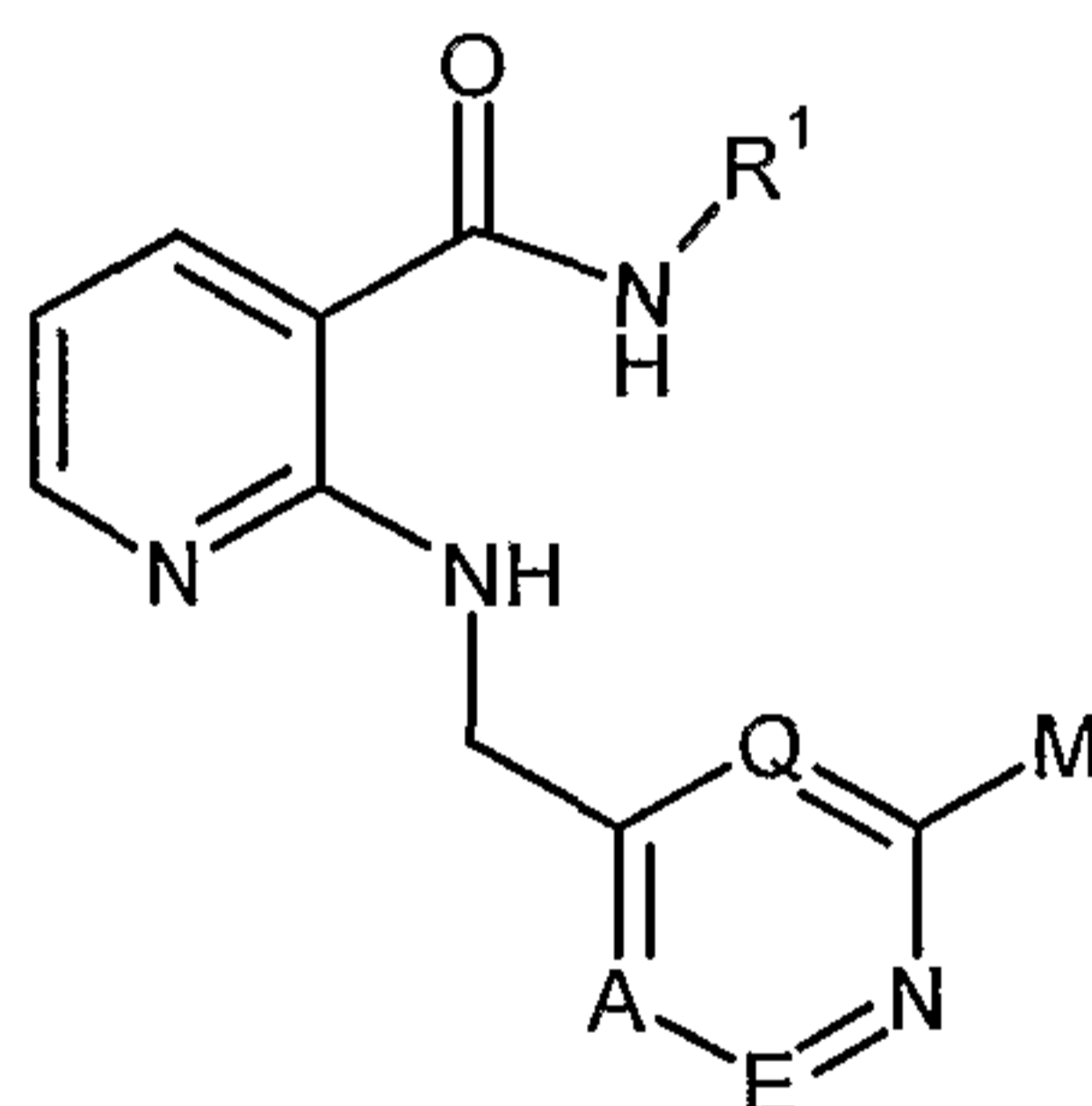
defined for formula (I) *supra* and R^y is H or C_1 - C_6 -alkyl, or of a compound of general formula (IIIA), in which A, E, Q, M, and R^1 are as defined for formula (I) *supra*, as an intermediate for the preparation of a compound of formula (I), *supra*.

5

In a thirteenth aspect of the present invention, there is provided a process for the preparation of a compound of formula (I), wherein all substituents are as described in claim 1, in which a compound of formula (III), wherein A, E, Q, R^2 , R^3 and R^9 are as defined in claim 1 and R^y is H or C_1 - C_6 -alkyl, is reacted
10 with an amine of formula R^1NH_2 in which R^1 is as defined in claim 1.

In a fourteenth aspect of the present invention, there is provided a process for the preparation of a compound of formula (I), wherein all substituents are as described in claim 1, in which a compound of formula (II) :

15



25

(II),

30

wherein A, E, Q, and R^1 are as defined in claim 1 and M stands for halogen, is :

- (i) first converted to an amine and subsequently converted to a compound of formula (I) by reaction with a carbamoyl chloride of formula $ClCONR^2R^3$, wherein R^2 and R^3 are as defined in claim 1; or,
35 alternatively,
- (ii) reacted with a compound of formula $R^9HNCONR^2R^3$, wherein R^2 , R^3 and R^9 are as defined in claim 1, or, alternatively,

(iii) first converted to an amine and subsequently converted to a compound of formula (I) by first reacting with a compound of formula ClCO_2Ph and then reacting with a compound of formula HNR^2R^3 , wherein R^2 and R^3 are as defined in claim 1. Preferably a compound of formula (I) is prepared using the (ii) process.

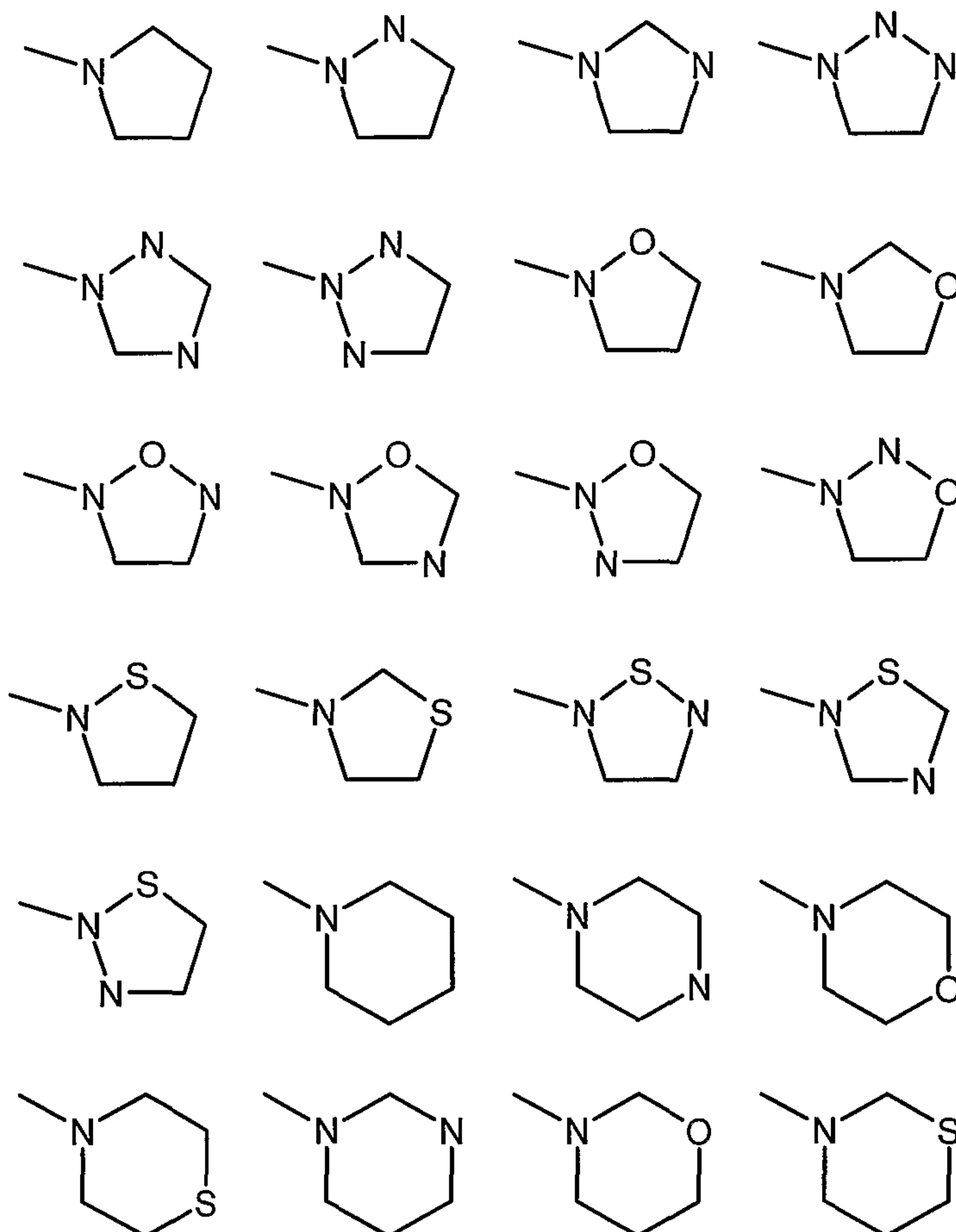
As used herein, the term "alkyl" is defined in each case as a substituted or unsubstituted straight-chain or branched alkyl group, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl or hexyl, heptyl, octyl, nonyl, decyl, undecyl, or dodecyl.

As used herein, the term "alkoxy" is defined in each case as a straight-chain or branched alkoxy group, such as, for example, methyloxy, ethyloxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, tert-butyloxy, pentyloxy, isopentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy, undecyloxy or dodecyloxy.

As used herein, the term "cycloalkyl" is defined as a monocyclic alkyl ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, and also as bicyclic rings or tricyclic rings, such as, for example, adamantanyl. The cycloalkyl group may also contain, one or more heteroatoms, such as oxygen, sulphur and/or nitrogen, such that a heterocycloalkyl ring is formed.

As used herein, the term "heterocycloalkyl", as used throughout this text, e.g. as used in the definition of " R^2 and R^3 together with the nitrogen atom to which they are attached form a 3-8 membered heterocycloalkyl ring" is defined as a nitrogen atom-containing monocyclic alkyl ring which optionally contains at least one further heteroatom, such as oxygen, sulphur and/or nitrogen, it being understood that said nitrogen atom links the heterocycloalkyl ring to the rest of the molecule. Preferred are 3-8 membered heterocycloalkyl rings, more preferably 4-7 membered heterocycloalkyl rings.

Even more preferred are 5 or 6 membered heterocycloalkyl rings. For example, a heterocycloalkyl ring such as one selected from the following list can be mentioned :



5

It is understood that any of the above structures may contain at least one additional heteroatom, such as nitrogen, oxygen or sulphur.

- 10 In particular, the following heterocycloalkyl rings can be mentioned: tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine, morpholine, piperazine and thiomorpholine. The heterocycloalkyl ring may be optionally substituted in one or more places in the same way or differently with, for example, halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O,
- 15 -OR⁵, -SR⁴, -SOR⁴ or -SO₂R⁶, -COR⁶, -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵. It is understood that the substitution

on any of the above-mentioned heterocycloalkyl rings may take place on any one of the heterocycloalkyl ring's carbon atoms and/or on any one of the heterocycloalkyl ring's heteroatoms. Preferably the heterocycloalkyl ring is substituted in one or two places.

5

As used herein, the term "halogen" is defined in each case as fluorine, chlorine, bromine or iodine, with fluorine being preferred for compounds of formula (I) and chlorine and bromine being preferred as substituent M in compounds of formula (II), (III), or (IIIA).

10

As used herein, the term "halo-C₁-C₆-alkyl" is defined as a C₁-C₆ alkyl group wherein some or all hydrogen atoms are replaced by halogen atoms, preferably replaced by one or more fluoro atoms. Preferred is the group CF₃.

15

As used herein, the term "alkenyl" is defined in each case as a straight-chain or branched alkenyl group that contains 2-6, preferably 2-4 carbon atoms. For example, the following groups can be mentioned: vinyl, propen-1-yl, propen-2-yl, but-1-en-1-yl, but-1-en-2-yl, but-2-en-1-yl, but-2-en-2-yl, 2-methyl-prop-2-en-1-yl, 2-methyl-prop-1-en-1-yl, but-1-en-3-yl, but-3-en-1-yl, and allyl.

20

As used herein, the term "aryl" is defined in each case as having 3-12 carbon atoms, preferably 6-12 carbon atoms, such as, for example, cyclopropenyl, cyclopentadienyl, phenyl, troyl, cyclooctadienyl, indenyl, naphthyl, azulenyl, biphenyl, fluorenyl, anthracenyl etc, phenyl being preferred.

25

As used herein, the term "C₁-C₁₂", as used throughout this text e.g. in the context of the definitions of "C₁-C₁₂-alkyl" and "C₁-C₁₂-alkoxy", is to be understood as meaning an alkyl or alkoxy group having a finite number of carbon atoms of 1 to 12, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. It is to be understood further that said term "C₁-C₁₂" is to be interpreted as any subrange comprised therein, e.g. C₁-C₁₂, C₂-C₁₁, C₃-C₁₀,

30

C₄-C₉, C₅-C₈, C₆-C₇, C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆, C₁-C₇, C₁-C₈, C₁-C₉, C₁-C₁₀, C₁-C₁₁; preferably C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; more preferably C₁-C₃.

- 5 Similarly, as used herein, the term "C₂-C₆", as used throughout this text e.g. in the context of the definitions of "C₂-C₆-alkenyl", is to be understood as meaning an alkenyl group having a finite number of carbon atoms of 2 to 6, i.e. 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C₂-C₆" is to be interpreted as any subrange comprised therein, e.g. C₂-C₆,
10 C₃-C₅, C₃-C₄, C₂-C₃, C₂-C₄, C₂-C₅; preferably C₂-C₃.

Further as used herein, the term "C₁-C₆", as used throughout this text e.g. in the context of the definitions of "halo-C₁-C₆-alkyl", is to be understood as meaning a haloalkyl group having a finite number of carbon atoms of 1 to 6,
15 i.e. 1, 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C₁-C₆" is to be interpreted as any subrange comprised therein, e.g. C₁-C₆, C₂-C₅, C₃-C₄, C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; more preferably C₁-C₃.

As used herein, the term "heteroaryl" as defined in each case, is an aromatic
20 ring system which contains, in the ring, at least one heteroatom which contains at least one heteroatom which may be identical or different, and which comprises 3-16 ring atoms, preferably 5 or 6 or 9 or 10 atoms, said heteroatom being such as oxygen, nitrogen or sulphur, and can be monocyclic, bicyclic, or tricyclic, and in addition in each case can be benzocondensed.
25 Preferably, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, etc., and benzo derivatives thereof, such as, e.g., benzofuranyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, etc.; or pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc.,
30 and benzo derivatives thereof, such as, e.g., quinolinyl, isoquinolinyl, etc.; or azocinyl, indolizinyl, purinyl, etc., and benzo derivatives thereof; or

cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, or oxepinyl, etc. More preferably the heteroaryl is selected from quinolinyl, isoquinolinyl, or indazolyl. More preferably still, the heteroaryl is
5 indazolyl.

The aryl group and the heteroaryl group in each case can be substituted in the same way or differently in one or more places with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴,
10 -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸. It is understood that the substitution on the aryl group and the heteroaryl group may take place on any one of the group's carbon atoms and/or on any one of the heteroatoms. Preferably the aryl group and the heteroaryl group is substituted in one or two places.

15

If an acid group is included, the physiologically compatible salts of organic and inorganic bases are suitable as salts, such as, for example, the readily soluble alkali salts and alkaline-earth salts as well as N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, 1,6-hexadiazine, ethanolamine,
20 glucosamine, sarcosine, serinol, tris-hydroxy-methyl-amino-methane, aminopropanediol, Sova base, and 1-amino-2,3,4-butanetriol.

If a basic group is included, the physiologically compatible salts of organic and inorganic acids are suitable, such as hydrochloric acid, sulphuric acid,
25 phosphoric acid, citric acid, tartaric acid, succinic acid, fumaric acid.

The compounds of general formula (I) according to the invention also contain the possible tautomeric forms and comprise the E-isomers or Z-isomers, or, if one or more stereogenic centers are present, racemates and/or enantiomers
30 and/or diastereoisomers. Thus, a molecule with a single stereogenic center may be a mixture of enantiomers (*R,S*), or may be a single (*R*) or (*S*)

enantiomer. A molecule with more than one stereogenic center may be a mixture of diastereoisomers, or may be a single diastereoisomer, whereby the diastereoisomers may also exist as mixtures of enantiomers or single enantiomers.

5

One embodiment of the present invention are compounds of formula (I) wherein A, E, and Q are each CH.

In one embodiment, R¹ is aryl or heteroaryl, which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₃-C₆-cycloalkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, aralkyloxy, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, cyano-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -OR⁵ or -NR⁷R⁸. In another embodiment, R¹ is phenyl, isoquinoliny, quinoliny or indazolyl optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₃-C₆-cycloalkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, aralkyloxy, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, cyano-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -OR⁵ or -NR⁷R⁸. In a preferred embodiment, R¹ is indazolyl substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₃-C₆-cycloalkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, aralkyloxy, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, cyano-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -OR⁵ or -NR⁷R⁸. In a more preferred embodiment, R¹ is indazolyl substituted with C₁-C₁₂-alkyl, optionally having a halogen atom substituent, preferably a fluorine, chlorine, bromine, or iodine atom. In an even more preferred embodiment, R¹ is indazolyl substituted with -CH₃. In an even more particularly preferred embodiment, R¹ is 2-methyl-indazolyl.

30 In one embodiment, R², R³ and R⁹ independently of one another, are hydrogen or C₁-C₁₂ alkyl optionally substituted with halogen, -OR⁵, or C₁-C₁₂-alkoxy. In a

preferred embodiment R^2 , R^3 and R^9 independently of one another, are hydrogen or C_1 - C_{12} alkyl. In a more preferred embodiment R^2 and R^3 independently of one another are hydrogen or $-CH_3$ and R^9 is hydrogen.

5 In another embodiment, R^9 is hydrogen and R^2 and R^3 together with the nitrogen atom to which they are attached form a 3-8 membered heterocycloalkyl ring, preferably a 4-7 membered heterocycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulphur, and which may be optionally substituted in one or more places in the
 10 same way or differently with halogen, cyano, C_1 - C_{12} -alkyl, C_1 - C_{12} -alkoxy, halo- C_1 - C_6 -alkyl, $=O$, $-OR^5$, $-SR^4$, $-SOR^4$, $-SO_2R^6$, $-COR^6$, or $-CO_2R^6$, whereby C_1 - C_{12} alkyl optionally can also be substituted with a group $-OR^5$. In a preferred embodiment, R^9 is hydrogen and R^2 and R^3 together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl ring, which
 15 contains no or at least one further heteroatom, such as nitrogen, oxygen or sulphur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C_1 - C_{12} -alkyl, C_1 - C_{12} -alkoxy, halo- C_1 - C_6 -alkyl, $=O$, $-OR^5$, $-SR^4$, $-SOR^4$, $-SO_2R^6$, $-COR^6$, or $-CO_2R^6$, whereby C_1 - C_{12} alkyl optionally can also be substituted with a group $-OR^5$.

20

In another embodiment, R^3 is hydrogen or C_1 - C_{12} -alkyl, whereby C_1 - C_{12} alkyl optionally can also be substituted with a group $-OR^5$ and R^2 and R^9 together with the two nitrogen atoms to which they are attached form a 5-7 membered ring, preferably a 5 or 6 membered ring, which may be optionally further
 25 substituted in one or more places in the same way or differently with halogen, C_1 - C_{12} -alkyl, C_1 - C_{12} -alkoxy, halo- C_1 - C_6 -alkyl, or $=O$, whereby C_1 - C_{12} alkyl optionally can also be substituted with a group $-OR^5$. In a preferred embodiment, R^3 is hydrogen or $-CH_3$ and R^2 and R^9 together with the two nitrogen atoms to which they are attached form a 5-7 membered saturated
 30 ring, preferably a 5 or 6 membered saturated ring, which may be optionally further substituted in one or more places in the same way or differently with

halogen, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, or =O, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵. In a more preferred embodiment, R³ is hydrogen and R² and R⁹ together with the two nitrogen atoms to which they are attached form a 5 membered saturated ring optionally further substituted in one or more places in the same way or differently with halogen, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, or =O, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵.

In one embodiment, R⁴ is C₁-C₁₂-alkyl. In a preferred embodiment, R⁴ is -CH₃.

10

In one embodiment, R⁵ is -CH₃ or hydrogen. In a preferred embodiment, R⁵ is hydrogen.

In one embodiment, R⁶ is C₁-C₁₂-alkyl or -NR⁷R⁸. In a preferred embodiment, R⁶ is C₁-C₁₂-alkyl. In a more preferred embodiment, R⁶ is -CH₃.

15

In one embodiment, R⁷ and R⁸ independently of one another, are hydrogen, COR⁶, SO₂R⁶, C₁-C₁₂-alkyl. In a preferred embodiment, R⁷ and R⁸ independently of one another are hydrogen or -CH₃.

20

Some specific examples of compounds of the present invention include the following:

N-(2-methyl-2H-indazol-6-yl)-2-{{2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino}-nicotinamide,

25

2-{{2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino}-N-(3-trifluoromethyl-phenyl)-nicotinamide,

N-(1-methyl-1H-indazol-6-yl)-2-{{2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino}-nicotinamide,

N-isoquinolin-3-yl-2-{{2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino}-nicotinamide,

30

N-(1-methyl-1H-indazol-5-yl)-2-{{2-(3-methyl-ureido)-pyridin-4-ylmethyl}-
 amino}-nicotinamide,
 morpholine-4-carboxylic acid (4-{{3-(2-methyl-2H-indazol-6-ylcarbamoyl)-
 pyridin-2ylamino]-methyl}-pyridin-2-yl)-amide,
 5 2-{{2-(3,3-dimethyl-ureido)-pyridin-4-ylmethyl]-amino}-N-(2-methyl-2H-
 indazol-6-yl)-nicotinamide,
 N-(2-methyl-2H-indazol-6-yl)-2-({2-[3-(1-methyl-piperidin-4-yl)-ureido]-
 pyridin-4-ylmethyl}-amino)-nicotinamide, and
 N-(2-methyl-2H-indazol-6-yl)-2-{{2-(2-oxo-imidazolidin-1-yl)-pyridin-4-
 10 ylmethyl]-amino}-nicotinamide ;

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

The compounds of formula (I) can be used as pharmaceutical agents based on
 their inhibitory activity relative to the phosphorylation of VEGF receptors.
 15 Based on their profile of action, the compounds according to the invention are
 suitable for preventing or treating diseases that are caused or promoted by
 persistent angiogenesis.

Since the compounds of formula (I) are identified as inhibitors of the tyrosine
 20 kinases VEGFR-1 and VEGFR-2, they are suitable in particular for preventing or
 treating those diseases that are caused or promoted by persistent angiogenesis
 that is triggered via the VEGF receptor or by an increase in vascular
 permeability.

25 The present invention also provides the use of the compounds of formula (I) as
 inhibitors of the tyrosine kinases VEGFR-1 and VEGFR-2, or KDR and FLT.

The term "diseases that are caused or promoted by persistent angiogenesis"
 relates especially to diseases such as tumor or metastasis growth, psoriasis,
 30 Kaposi's sarcoma, restenosis, such as, e.g., stent-induced restenosis,
 endometriosis, Crohn's disease, Hodgkin's disease, leukemia; arthritis, such as

rheumatoid arthritis, hemangioma, angiofibroma; eye diseases, such as diabetic retinopathy, neovascular glaucoma; corneal transplants; renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndrome, transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver, mesangial cell proliferative diseases, arteriosclerosis, injuries to nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents, as immunosuppressive agents, for supporting scar-free healing, in senile keratosis, in contact dermatitis, and in asthma.

In treating injuries to nerve tissue, quick scar formation on the injury sites can be prevented with the compounds according to the invention, i.e., scar formation is prevented from occurring before the axons reconnect. A reconstruction of the nerve compounds can be thus facilitated.

The formation of ascites in patients, especially patients suffering from tumors caused by metastases, can also be suppressed with the compounds according to the invention. VEGF-induced oedemas can also be suppressed.

By a treatment with the compounds of formula (I), not only a reduction of the size of metastases but also a reduction of the number of metastases can be achieved.

Lymphangiogenesis plays an important role in lymphogenic metastasis (Karpanen, T. et al., *Cancer Res.* 2001 Mar 1; 61(5): 1786-90, Veikkola, T., et al., *EMBO J.* 2001, Mar 15; 20 (6): 1223-31).

The compounds of formula (I) also show excellent action as VEGFR kinase 3 inhibitors and are, therefore, also suitable as effective inhibitors of lymphangiogenesis.

The compounds of formula (I) are thus effective in the prevention or treatment of diseases that are associated with excessive lymphangiogenesis, such as lymphedema, lymphangiectasia, lymphangioma, and lymphangiosarcoma but also asthma. Lymphatic growth around tumors may facilitate metastatic spread of malignant cells that ultimately kill the patient. This process can be effectively hindered by the compounds of this invention. Thus the compounds are not only effective in inhibiting metastasis growth, but can also be effective in reducing the number of metastases.

10

This invention also provides the use of the compounds of formula (I) as inhibitors of the tyrosine kinase VEGFR-3 (FLT-4).

A further object of this invention is also a pharmaceutical agent for preventing or treating diseases that are associated with excessive lymphangiogenesis, such as metastasis growth, lymphedema, lymphangiectasia, lymphangioma, and lymphangiosarcoma but also asthma.

Furthermore, the invention relates to the use of the compounds of general formula (I) for the preparation of a pharmaceutical agent for use in or for the prevention or treatment of tumor or metastasis growth, psoriasis, Kaposi's sarcoma, restenosis, such as, e.g., stent-induced restenosis, endometriosis, Crohn's disease, Hodgkin's disease, leukemia; arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma; eye diseases, such as diabetic retinopathy, neovascular glaucoma; corneal transplants; renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver, mesangial cell proliferative diseases, arteriosclerosis, injuries to nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open,

30

such as, e.g., stents, as immunosuppressive agents, for supporting scar-free healing, in senile keratosis, in contact dermatitis, and also in asthma.

To use the compounds of formula (I) as pharmaceutical agents, the latter are brought into the form of a pharmaceutical preparation, which in addition to the active ingredient for enteral or parenteral administration contains suitable pharmaceutical, organic or inorganic inert carrier materials, such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, etc. The pharmaceutical preparations can be present in solid form, for example as tablets, coated tablets, suppositories, capsules or in liquid form, for example as solutions, suspensions or emulsions. They also can contain, moreover, adjuvants such as preservatives, stabilizers, wetting agents or emulsifiers, salts for changing osmotic pressure or buffers.

15

For parenteral administration, especially injection solutions or suspensions, especially aqueous solutions of the active compounds in polyhydroxyethoxylated castor oil, are suitable.

As carrier systems, surface-active adjuvants such as salts of bile acids or animal or plant phospholipids, but also mixtures thereof as well as liposomes or components thereof can also be used.

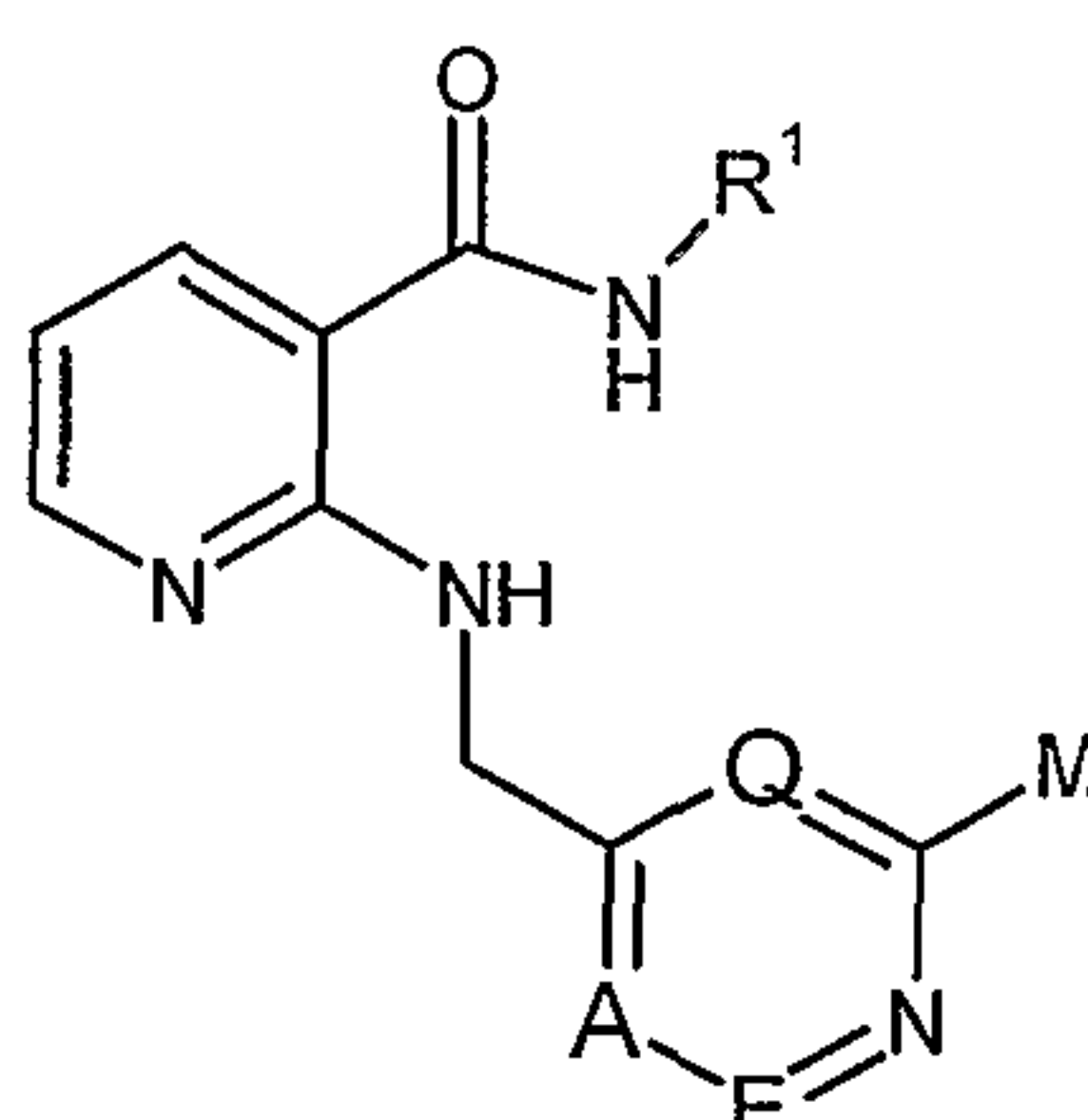
For oral administration, especially tablets, coated tablets or capsules with talc and/or hydrocarbon vehicles or binders, such as for example, lactose, corn starch or potato starch, are suitable. The administration can also be carried out in liquid form, such as, for example, as juice, to which optionally a sweetener or, if necessary, one or more flavouring substances, is added.

The dosage of the active ingredients can vary depending on the method of administration, age and weight of the patient, type and severity of the

disease to be treated and similar factors. The daily dose is 0.5-1000 mg, preferably 50-200 mg, whereby the dose can be given as a single dose to be administered once or divided into 2 or more daily doses.

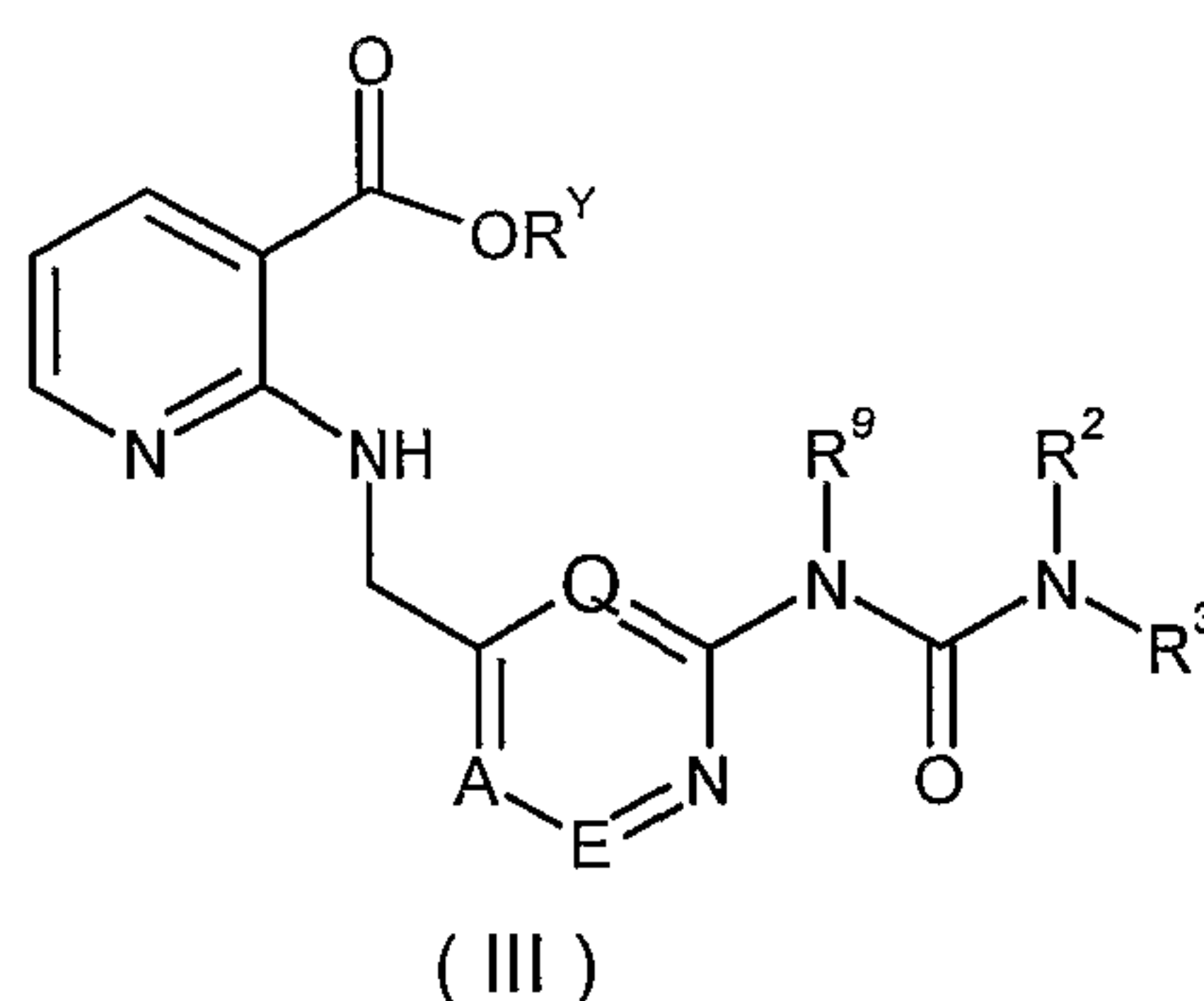
- 5 A further object of this invention is therefore a pharmaceutical agent comprising a compound of formula (I) in combination with at least one pharmaceutically acceptable carrier or excipient.

Compounds of formula (I) are obtained, in that a compound of general formula
10 (II) :



(II),

in which A, E, Q, and R¹ are defined *supra* as for general formula (I) and M
15 stands for halogen, is (i) first converted to an amine and then, by reaction with a carbamoyl chloride of formula ClCONR²R³ in which R² and R³ are defined *supra* as for general formula (I), is converted to a urea of general formula (I), or (ii) reacted with a urea of general formula R⁹HNCONR²R³ in which R², R³ and R⁹ are defined *supra* as for general formula (I), or (iii) first converted to an
20 amine, then converted to a compound of formula (I) by first reacting with a compound of formula ClCO₂Ph and then reacting with a compound of formula HNR²R³, wherein R² and R³ are defined *supra* as for general formula (I); or a compound of general formula (III) in which A, E, Q, R², R³ and R⁹ are defined as for general formula (I) and R^Y stands for H or C₁-C₆-alkyl, is reacted with an
25 amine of general formula R¹NH₂ in which R¹ is defined *supra* as for general formula (I) :



There are many methods known to the person skilled in the art in the literature for amide formation. For example, it is possible to start from the corresponding ester. The ester may be reacted according to J. Org. Chem. 1995, 8414 with trimethylaluminium and the corresponding amine in solvents such as toluene, at temperatures of 0°C to the boiling point of the solvent. If the molecule contains two ester groups, both are converted into the same amide. Instead of trimethylaluminium, sodium hexamethyldisilazide can also be used.

For amide formation, however, all processes that are known to the person skilled in the art from peptide chemistry are also available. For example, the corresponding acid, obtained from the corresponding ester by saponification, can be reacted with the amine in aprotic polar solvents, such as, for example, dimethylformamide, via an activated acid derivative, obtainable, for example, with hydroxybenzotriazole and a carbodiimide, such as, for example, diisopropylcarbodiimide, at temperatures of between 0°C and the boiling point of the solvent, preferably at 80°C, or else with preformed reagents, such as, for example, HATU (O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (Chem. Comm. 1994, 201), at temperatures of between 0°C and the boiling point of the solvent, preferably at room temperature. The addition of a base such as N-methylmorpholine, for example, is necessary. Amide formation, may also be accomplished via the acid halide, mixed acid anhydride, imidazolide or azide.

The ureas of aryl- or heteroaryl amines may be prepared by a variety of literature known methods, known to the person skilled in the art. For example, they may be prepared by the reaction of aryl- or heteroaryl amines with isocyanates, the reaction of amines with aryl- or heteroaryl-carbamates such as aryl- or heteroaryl-phenoxy-carbamates, or the reaction of aryl- or heteroaryl amines with appropriately substituted carbamoyl chlorides, or the reaction of an aryl- or heteroaryl-halide with ureas under the influence of metal catalysis.

10

For example, the ureas of aminopyridines may be prepared by reacting a urea with halopyridines, whereby chloro and bromopyridines are preferred, under the catalytic influence of metal complexes, for example, palladium- or copper complexes. In the case of copper complexes the use of stoichiometric amounts of the copper complexes may be advantageous for the reaction outcome. Suitable copper salts for the reaction are copper (I) or copper (II) salts whereby copper (I) salts such as, for example, copper (I) oxide or copper (I) iodide, are preferred. In the case of copper (I) iodide the addition of an additive such as, for example, ethylenediamine is necessary. Suitable solvents for this copper-promoted coupling are dioxane or dimethylformamide, at temperatures upto the boiling point of the solvents, whereby 120 °C is preferred. Addition of a base is also necessary, such as potassium phosphate or cesium carbonate. In the case of palladium catalysis, palladium complexes such as tris-(dibenzylideneacetone) -dipalladium(0) maybe employed. Suitable solvents for the reaction are toluene, dioxane or dimethylformamide, whereby mixtures of solvents may also be advantageous for the reaction, at temperatures from room temperature to the boiling points of the solvents, whereby 110°C is preferred. A co-ligand such as BINAP, DPPF or xantphos is also employed. A base is also required, suitable bases for the reaction are for example, cesium carbonate, potassium phosphate or sodium tert-butoxide.

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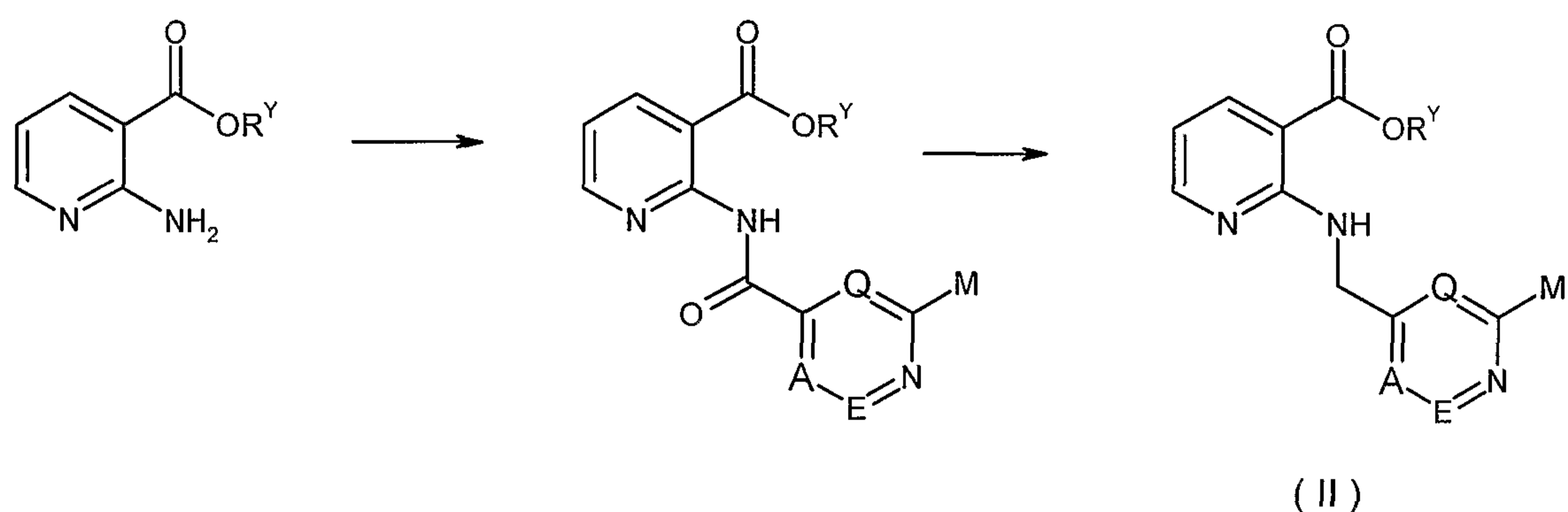
The required urea starting materials for the above copper or palladium promoted coupling may in turn be prepared from the reaction of the corresponding amines with the corresponding isocyanates. Solvents such as for example dichloromethane, or isopropylalcohol may be employed at
5 temperatures from 0°C to the boiling points of the solvents, whereby room temperature is preferred.

The required 2-amino-nicotinic acid esters (general formula II, Scheme 1) may be prepared by a variety of methods. For example, known 2-chloronicotinic
10 acid esters may be reacted with appropriately substituted amines at elevated temperatures whereby 120 °C is preferred. The reaction may be conducted without solvents. In turn, the amines may be obtained from the corresponding nitriles, for example, by hydrogenation in the presence of a suitable metal catalyst, such as Raney Nickel. Alternatively, the nitrile may be reduced with
15 metal hydride reagents such as, for example, lithium aluminium hydride. Similar reductions of aryl nitriles to benzylamines are well documented in the literature and are well known to the person skilled in the art. An alternative preparation of the required 2-amino-nicotinic acid esters is accomplished as outlined in Scheme 1, in which A, E, Q, R¹, R², R³, and R⁹ are defined in the
20 same way as for the general formula (I), M is halogen and R^Y is H or C₁-C₆-alkyl. Esterification of 2-aminonicotinic acid may be accomplished by a variety of well known techniques, well known to the person skilled in the art. Acylation with an appropriately substituted activated acid derivative, for example, the corresponding acid halides or anhydrides, whereby the acid
25 chloride is preferred, in inert solvents, for example, dichloromethane, with addition of tertiary amine bases, for example triethylamine, with cooling, whereby cooling at 0 °C is preferred, delivers the corresponding amide derivatives. The amides may be reduced to compounds of general formula (II) by employing a suitable reducing agent, for example a borane complex such as
30 borane-dimethyl sulphide complex, in solvents, for example, tetrahydrofuran,

at temperatures ranging from chilled to room temperature to the boiling point of the solvents, whereby room temperature is preferred.

Scheme 1

5



Methods for the preparation of substituted or unsubstituted 6-aminoindazoles are well known to the person skilled in the art, in the literature. They may be obtained from the reduction of the corresponding nitroindazoles via catalytic hydrogenation or other reduction methods well known to the person skilled in the art. N-alkylation of substituted nitroindazoles may be accomplished with a variety of literature-known alkylating agents. For example, methylation of N-1 or N-2 of a suitably functionalised 6-nitroindazole may be accomplished by for example treatment with a base, preferably Cs_2CO_3 or NaH , and a methyl halide, preferably methyl iodide in a suitable solvent such as N,N-dimethylformamide, at temperatures ranging from $0\text{ }^\circ\text{C}$ to $50\text{ }^\circ\text{C}$, whereby $50\text{ }^\circ\text{C}$ is preferred. 3-Substituted-6-nitroindazoles may be prepared by a variety of methods. For example alkyl substituents may be introduced in the 3-position by way of standard Suzuki reactions between an appropriate 3-haloindazole, whereby the appropriate 3-iodoindazoles are preferred, and an alkyl boronic acid, whereby the trialkylboraxines may also be employed. N-protection of the indazole may be advantageous for the reaction. 6-Nitroindazole-3-carboxylic acid provides a suitable starting material for ester, amide, hydroxymethyl and alkoxyethyl substitution in the 3-position of 6-

nitroindazole, via transformations well known to the person skilled in the art, such as transesterification, amide coupling, reduction, or reduction followed by alkylation. 6-Nitroindazole-3-carbaldehyde (prepared by the reaction of commercial 6-nitroindole with NaNO_2 in the presence of dilute aqueous hydrochloric acid according to J. Med. Chem. 2001, 44, 7, 1021) provides a useful precursor to 6-nitroindazole-3-carboxylic acid via well known oxidation methods. In turn 6-nitroindazole-3-carbaldehyde may also be converted to 3-hydroxymethyl-6-nitroindazole, 3-alkoxymethyl-6-nitroindazole, or 3-aminomethyl-6-nitroindazole derivatives by equally standard transformations such as reduction, reduction followed by alkylation, or reductive amination. Such standard transformations may also be applied to the synthesis of other substituted aminoindazoles. A variety of substituted nitroindazoles are commercially available, however they may be readily synthesised via the reaction of a suitable 2-amino-nitrotoluene derivative with, for example, NaNO_2 and aqueous hydrochloric acid. If required, the nitro group may be introduced after the cyclisation reaction of a suitable 2-aminotoluene derivative by standard nitration chemistry.

The preparation of N-alkylated-aminobenzimidazoles may be accomplished from the corresponding N-alkylated-nitrobenzimidazoles via standard reduction chemistry. Alkylation of a suitable functionalised nitrobenzimidazole, for example with an alkyl halide and a base, furnishes N1- and N3-alkylated-nitrobenzimidazoles, which may be separated and isolated in pure form by standard purification techniques. For example, 6-amino-1-methyl-benzimidazole may be produced by the reaction of commercial 5-nitrobenzimidazole with MeI and Cs_2CO_3 in DMF followed by purification (of the resulting mixture of 5- and 6-nitro-1-methyl-benzimidazoles) and hydrogenation in the presence of 10% Pd on charcoal. Similarly, the preparation of N-alkylated-aminobenzotriazoles may also be accomplished from the corresponding nitrobenzotriazoles. Alkylation of a suitable functionalised nitrobenzotriazole, for example with an alkyl halide and a base,

furnishes N1-, N2- and N3-alkylated-nitrobenzotriazoles, which may be separated and isolated in pure form by standard purification techniques. Standard reduction chemistry furnishes the corresponding aminobenzotriazoles. For example, 5-amino-2-methyl-benzotriazole may be prepared according to a literature procedure (Eur. J. Med. Chem. 1992, 27, 161-166).

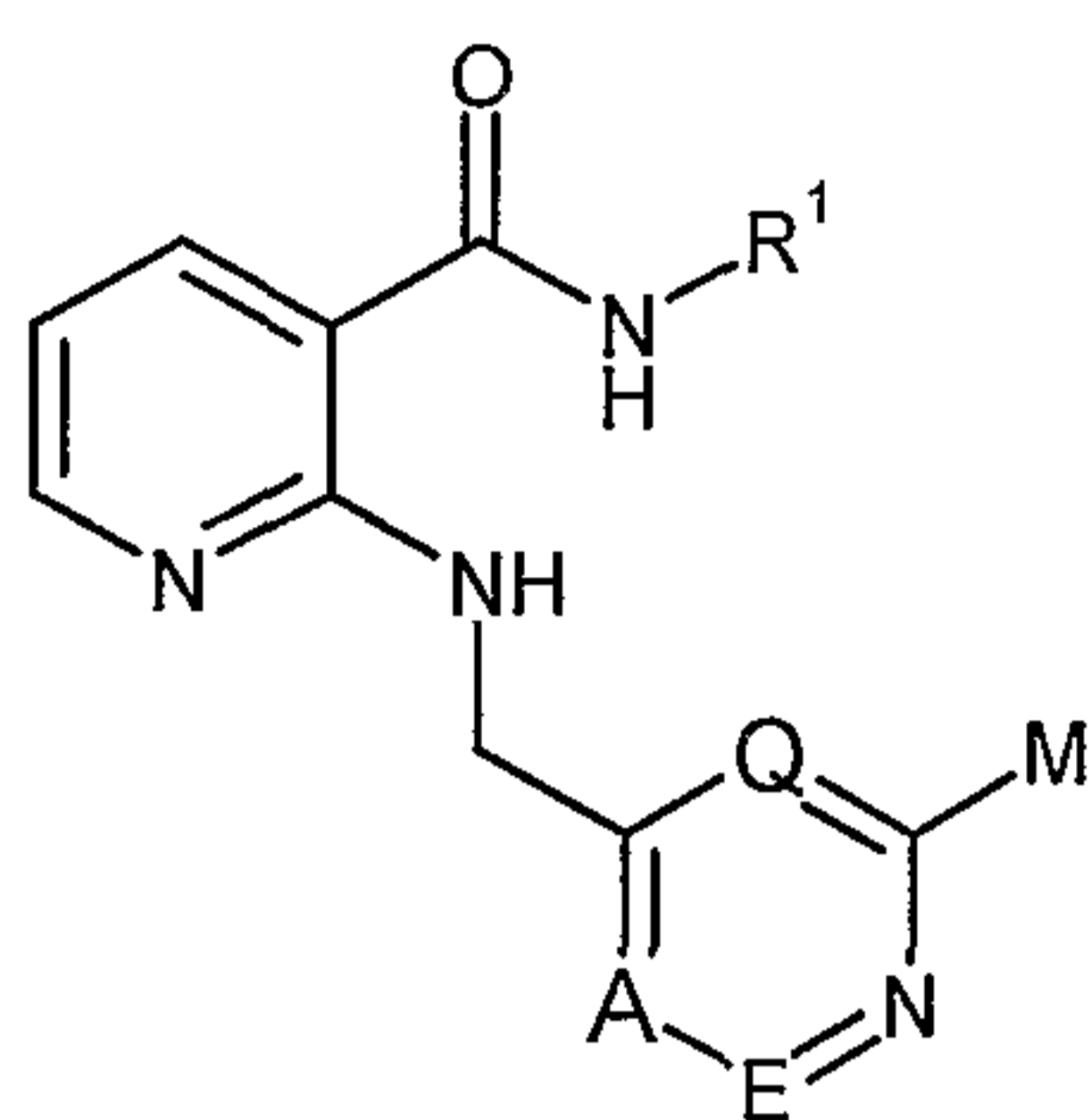
The preparation of 3-aminoisoquinolines which are substituted in the 7-position, may be accomplished via the corresponding 3-amino-1-bromo-7-substituted isoquinoline by way of reductive dehalogenation. 3-amino-1-bromo-7-substituted isoquinolines may in turn be prepared by the reaction of a suitable 2-cyano-4-substituted-benzeneacetonitrile with HBr in acetic acid. For example, 3-amino-7-methoxyisoquinoline may be prepared in two steps (HBr mediated cyclisation followed by reductive dehalogenation) from 2-cyano-4-methoxy-benzeneacetonitrile, which may be prepared according to a literature procedure (Bull. Chem. Soc. Jpn. 1980, 53, 10, 2885-2890).

1-Alkyl-6-amino-quinolin-2-ones may be prepared by methods known to the person skilled in the art. For example, 6-amino-2-methyl-quinolin-2-one may be prepared according to a literature procedure (J. Chem. Research, Synopses, 1997, 310-311).

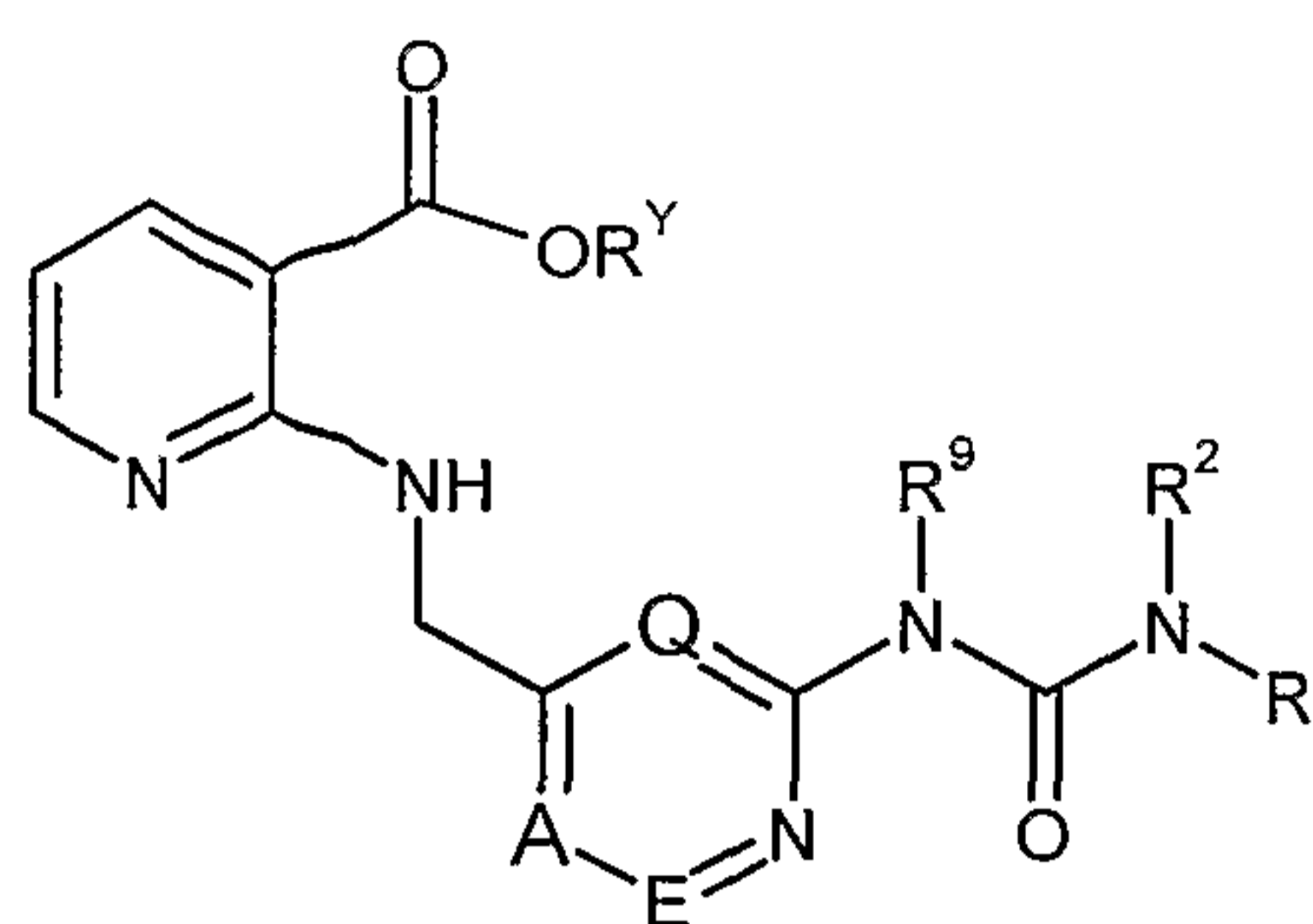
2-Amino-3,6-disubstituted quinolines may be prepared by a number of procedures. For example, the reaction of the lithium salt (generated with a base such as lithium diisopropylamide) of a suitably substituted cyanomethyl-dialkylphosphonate with a suitably substituted 2-nitrobenzaldehyde derivative in a suitable solvent, such as THF, furnishes a suitable acrylonitrile derivative which may be cyclised to the desired 2-amino-3,6-disubstituted quinoline by treating with a suitable reducing agent, such as iron in acetic acid.

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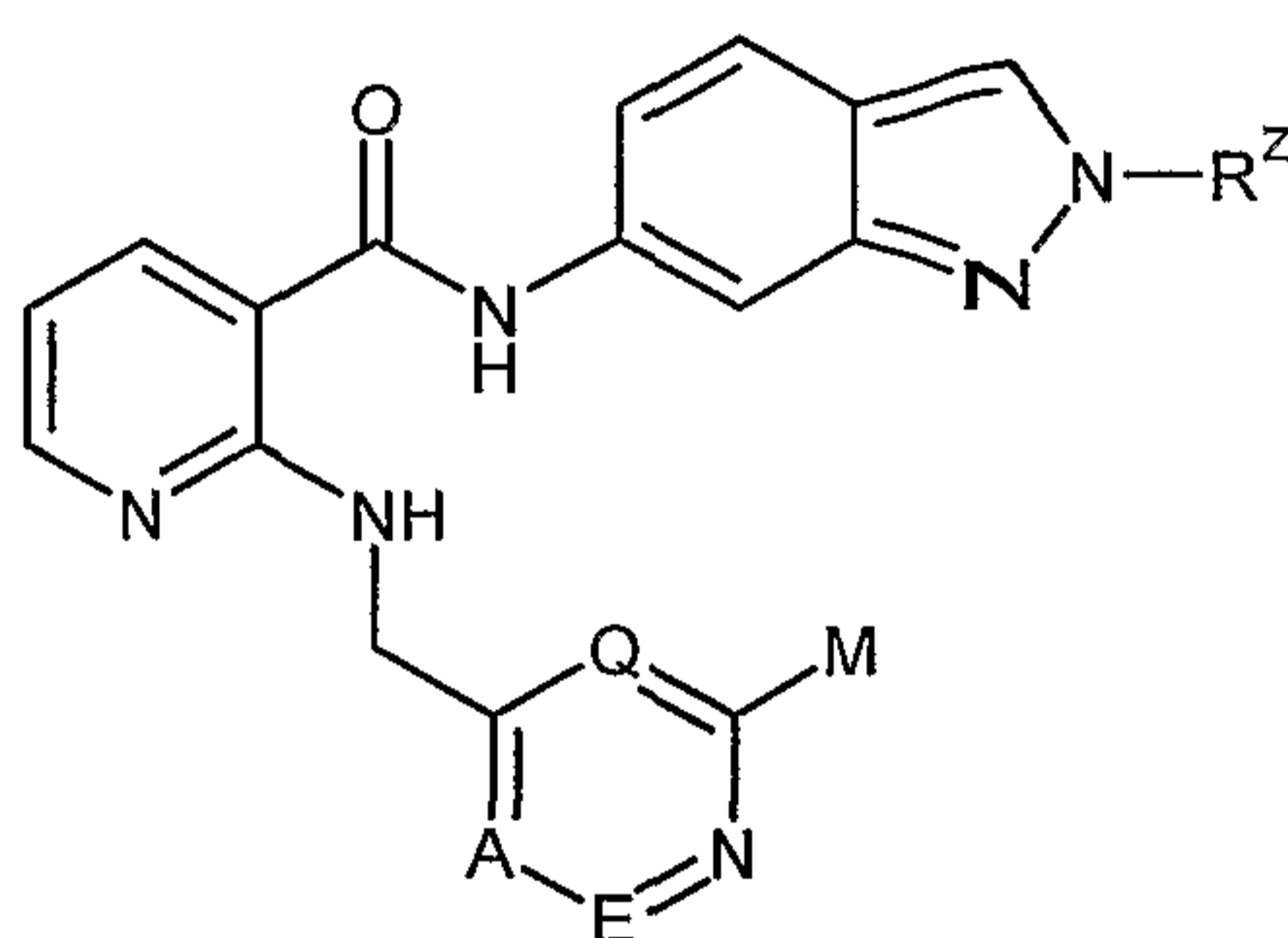
The compounds of the general formulae II, III, and IIIA :



(II),



(III),



(IIIA)

5

in which A, E, Q, R¹, R², R³, and R⁹ are defined in the same way as for the general formula (I), R^Z is C₁-C₁₂-alkyl, M is halogen and R^Y is H or C₁-C₆-alkyl, provide valuable intermediates for the preparation of the inventive compounds of general formula (I) and, are therefore also objects of the invention. The use of compounds of formula (II) and (III) in the production of a compound of formula (I), as well as the process described above using these compounds in the production of a compound of formula (I) are also objects of the invention.

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EXAMPLES

Production of the compounds according to the invention

- 5 The following examples explain the production of the compounds according to the invention without the scope of the claimed compounds being limited to these examples.

Abbreviations

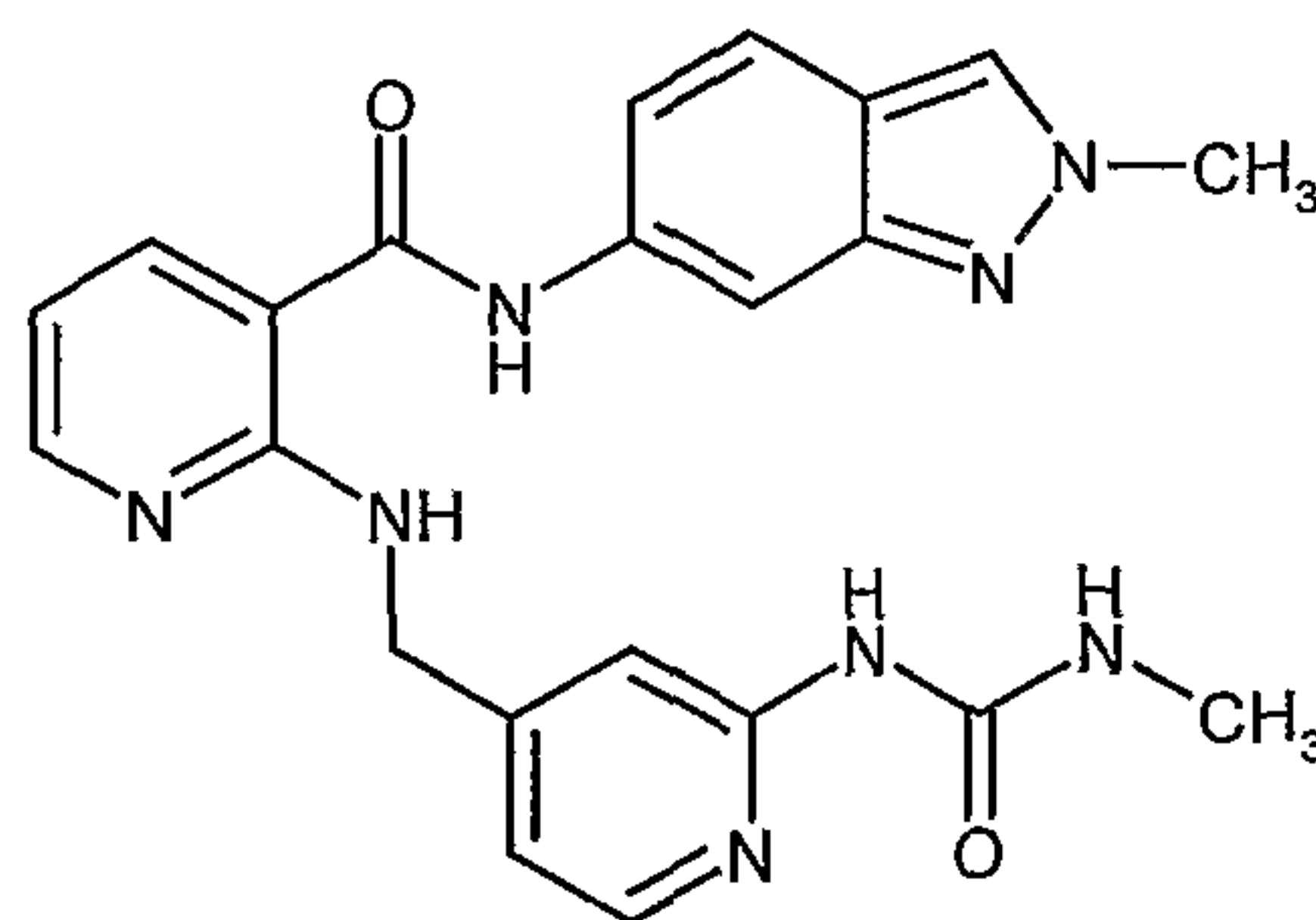
The following abbreviations used in the invention have the following meanings:

10	Brine	saturated aqueous sodium chloride solution
	CI+	chemical ionisation (NH ₃)
	DCE	1,2-dichloroethane
	DMF	N,N-dimethyl formamide
	d ₆ -DMSO	d ₆ -dimethylsulphoxide
15	d	doublet
	dd	doublet of doublets
	ES+	positive mode electrospray ionisation
	EtOAc	ethyl acetate
	EtOH	ethanol
20	¹ H-NMR	proton nuclear magnetic resonance spectroscopy : chemical shifts (δ) are given in ppm.
	Hex	n-hexane
	LC-ES+	liquid chromatography / positive mode electrospray ionisation
25	LDA	Lithium diisopropylamide
	MeOH	methanol
	m	multiplet
	Mp.	melting point
	MS	mass spectrometry
30	m/z	mass / charge ratio

Pd ₂ dba ₃	tris-(dibenzylideneacetone)-dipalladium(0)-chloroform complex
rt	room temperature
RT	retention time (LC)
5 s	singlet
THF	tetrahydrofuran
t	triplet
Xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

10 **Example 1.0**

Preparation of *N*-(2-methyl-2H-indazol-6-yl)-2-[[2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino]-nicotinamide



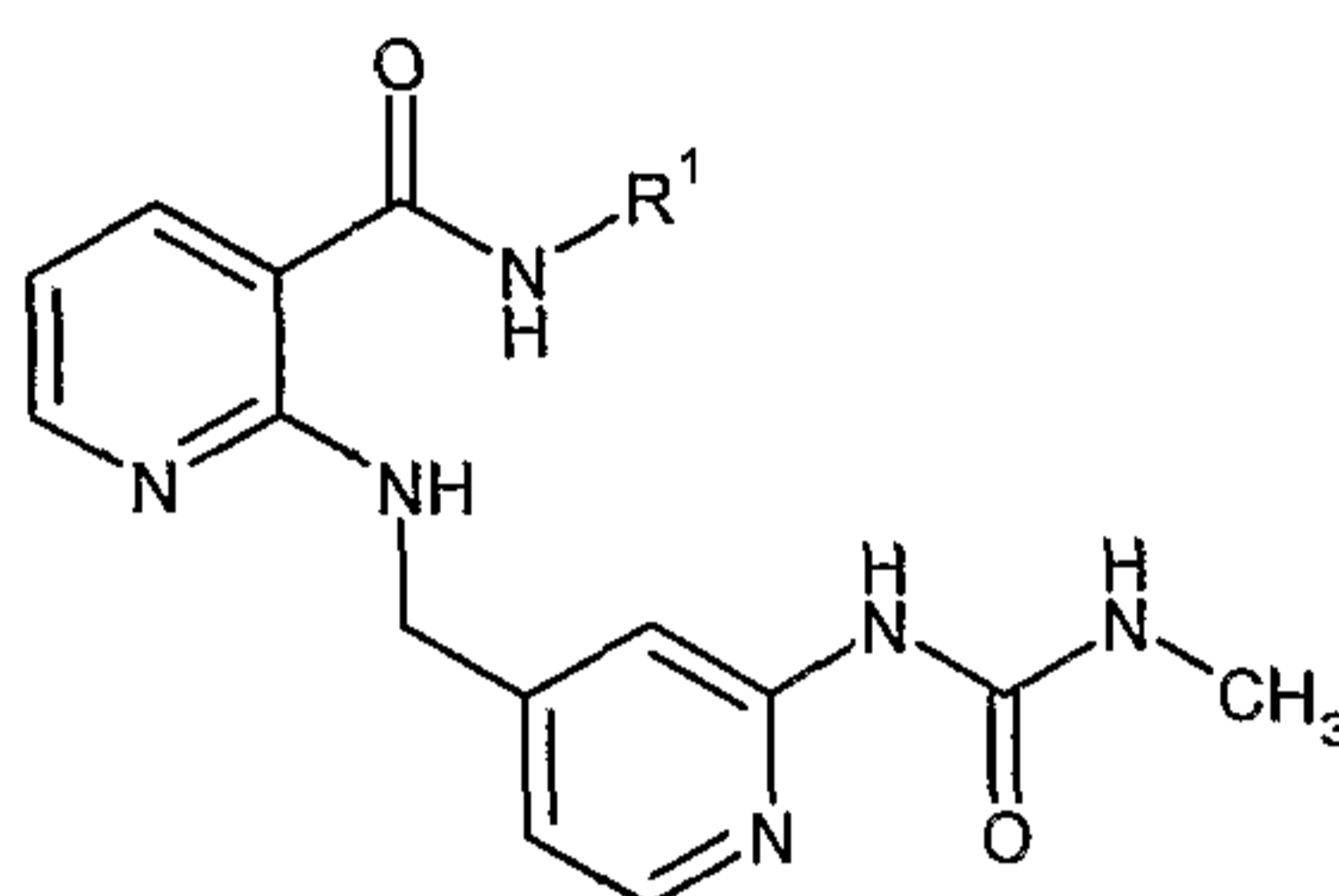
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A suspension of 2-methyl-2H-indazol-6-ylamine [Davies *J. Chem. Soc.*; **1955**; 2412-2419] (809 mg, 5.5 mmol) in DCE (13.5 mL) was treated at 0 °C consecutively with, trimethylaluminium (2 M) in toluene (4.23 mL, 8.46 mmol), 2-[[2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino]-nicotinic acid methyl ester (1.34 g, 4.23 mmol) and DCE (20 mL). The reaction mixture was placed under a nitrogen atmosphere and heated for 10 hours at 85 °C (bath temperature). On cooling the reaction was poured into aqueous sodium-potassium tartrate solution (150 mL) and partitioned between EtOAc and water. The organic phase was washed with brine, dried, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (Gradient elution: 100% CH₂Cl₂ to 90% CH₂Cl₂/10% MeOH) to give *N*-(2-

25

methyl-2H-indazol-6-yl)-2-{{2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino}-nicotinamide (964 mg, 53%) as a solid; Mp. 205-207 °C.

The following examples were prepared in analogy to Example 1 from 2-{{2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino}-nicotinic acid methyl ester and the corresponding amine:

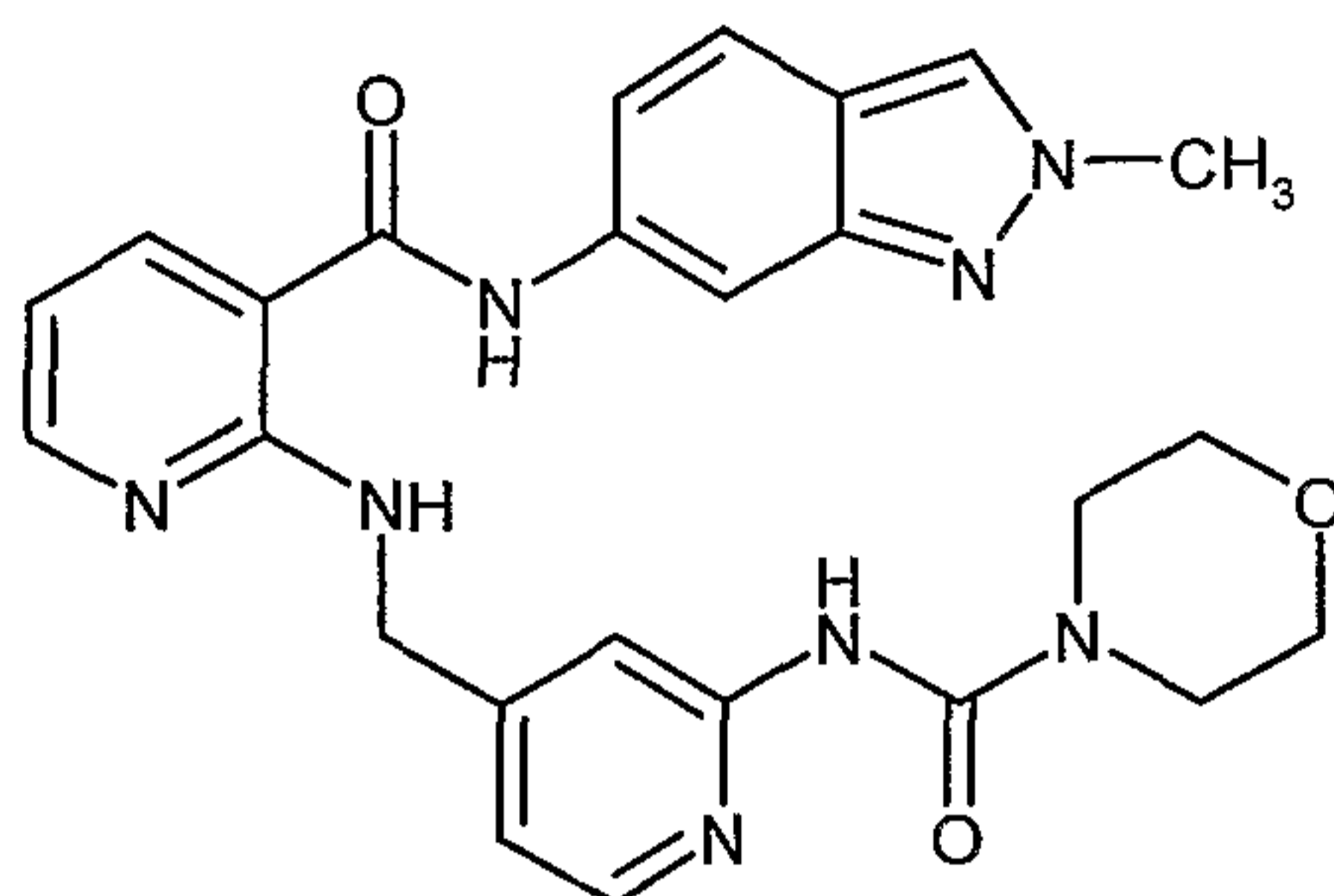


Example Nr.	R ¹	MW	Mp. [°C]
1.1		444.42	206-207
1.2		430.47	228-229
1.3		427.47	191-192
1.4		430.47	219-220

Example 2.0

Preparation of morpholine-4-carboxylic acid (4-[[3-(2-methyl-2H-indazol-6-ylcarbamoyl)-pyridin-2-ylamino]-methyl]-pyridin-2-yl)-amide

5



A mixture of 2-[(2-chloro-pyridin-4-ylmethyl)-amino]-N-(2-methyl-2H-indazol-6-yl)-nicotinamide (200 mg, 0.51 mmol), Pd₂dba₃ (5.2 mg, 0.0051 mmol), xantphos (9.1 mg, 0.0153 mmol), cesium carbonate (169 mg, 0.54 mmol) and morpholine-4-carboxylic acid amide (332 mg, 2.55 mmol) in dioxane (12.1 mL) and DMF (4.1 mL) under nitrogen, was stirred at 110 °C for 11 hours. A second reaction was performed in duplicate. The two reactions were combined, diluted with dilute aqueous sodium hydrogencarbonate solution and extracted with EtOAc. The combined organic layers were washed with brine, dried and concentrated *in vacuo*. Purification was achieved by chromatography on Isolute® flash silica gel (Separtis) to give morpholine-4-carboxylic acid (4-[[3-(2-methyl-2H-indazol-6-ylcarbamoyl)-pyridin-2-ylamino]-methyl]-pyridin-2-yl)-amide (119 mg) which was further purified by recrystallisation from EtOAc;

¹H-NMR (300 MHz, d₆-DMSO) 10.2 (1H, s), 9.06 (1H, s), 8.45 (1H, t), 8.22 (1H, s), 8.03-8.13 (4H, m), 7.73 (1H, s), 7.62 (1H, d), 7.27 (1H, unresolved dd), 6.89 (1H, unresolved dd), 6.67 (1H, dd), 4.62 (2H, d), 4.10 (3H, s), 3.52 (4H, t), 3.39 (4H, t).

The following examples were prepared in analogy to Example 2.0 from the corresponding 2-chloropyridine derivative and the corresponding urea:

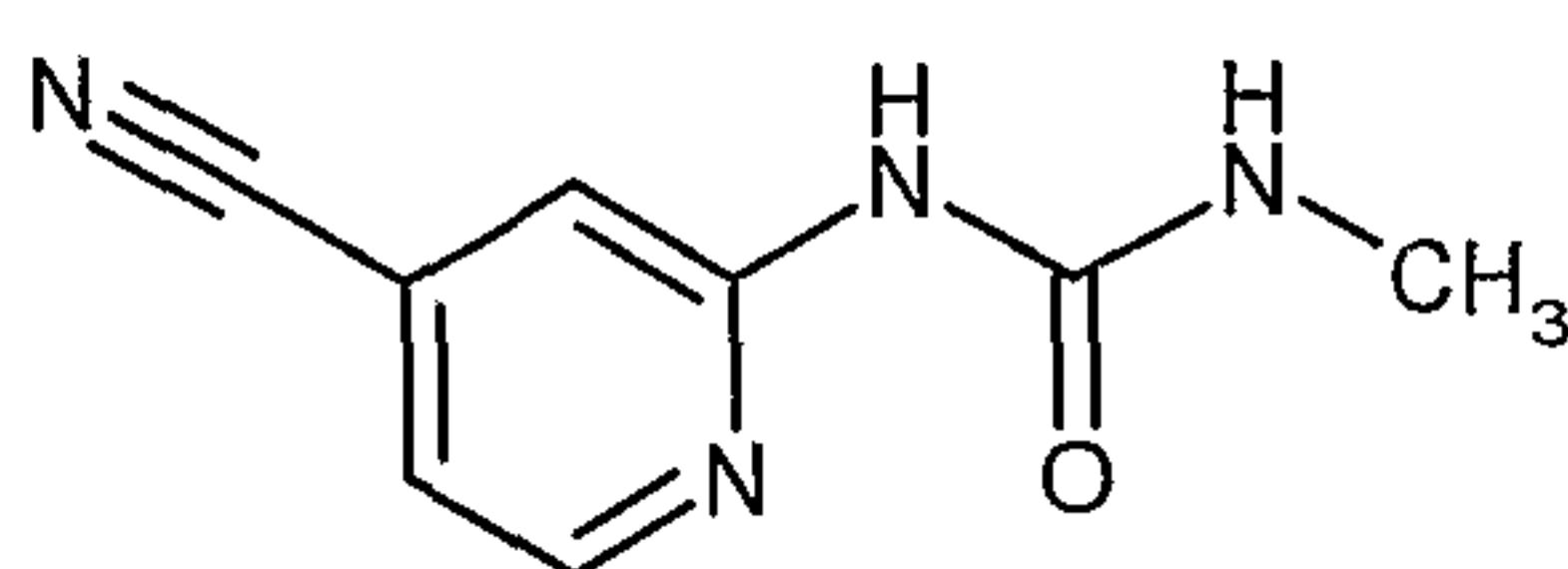
Production of Starting and Intermediate Compounds

If the production of the intermediate compounds is not described, the latter are known or can be produced analogously to known compounds or processes that are described here or in WO2004/013102.

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Example 3.1

Preparation of 1-(4-cyano-pyridin-2-yl)-3-methyl-urea



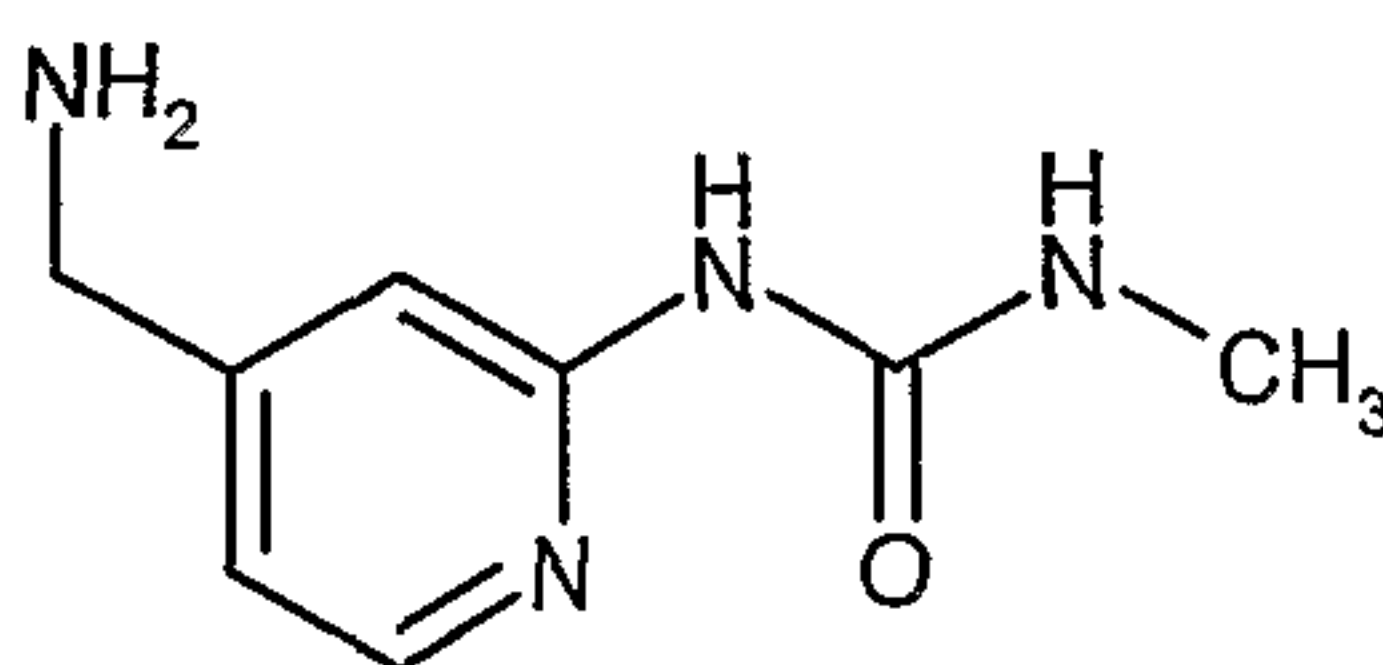
10

A mixture of 2-chloro-isonicotinonitrile [Talík et al. *Rocz. Chem.*; 29; 1955; 1019, 1025.] (13.9 g, 0.1 mol), Pd₂dba₃ (2.0 g, 2 mmol), Xantphos (3.6 g, 6.22 mmol), cesium carbonate (39.1 g, 120 mmol) and methylurea (37.04 g, 0.5 mol) in dioxane (800 mL), under a nitrogen atmosphere was heated for 8 hours at 130 °C (bath temperature). On cooling the reaction mixture was concentrated in vacuo. The residue was partitioned between CH₂Cl₂ and water. The organic phase was washed with brine, dried, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (gradient elution: 100% hexane to 100% EtOAc) to give 1-(4-cyano-pyridin-2-yl)-3-methyl-urea (12.1 g) as a solid; Mp. 203-204 °C.

20

Example 3.2

Preparation of 1-(4-aminomethyl-pyridin-2-yl)-3-methyl-urea

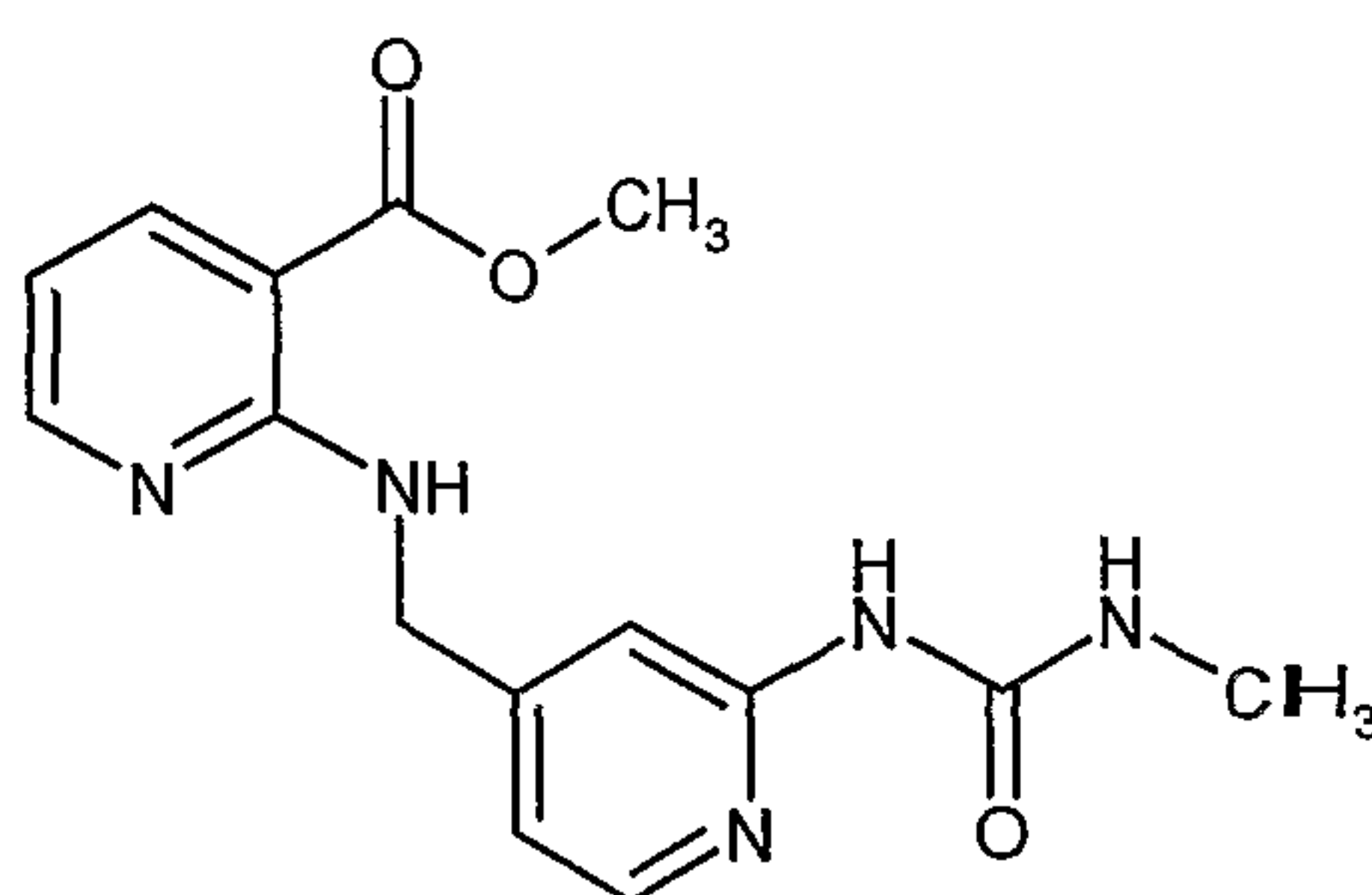


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A solution of 1-(4-cyano-pyridin-2-yl)-3-methyl-urea (12.0 g, 11.4 mmol) in THF (80 mL) was treated with Raney nickel (0.5 g) placed under a hydrogen atmosphere (atmospheric pressure) for 8 hours at rt. The reaction mixture was diluted with EtOAc, filtered over Celite® and concentrated in vacuo. The residue was purified by chromatography on silica gel (Gradient elution: 100% CH₂Cl₂ to 85% / 15% CH₂Cl₂ / MeOH) to give 1-(4-aminomethyl-pyridin-2-yl)-3-methyl-urea (4.8 g) as a solid.

Example 3.3

10 Preparation of 2-[[2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino]-nicotinic acid methyl ester

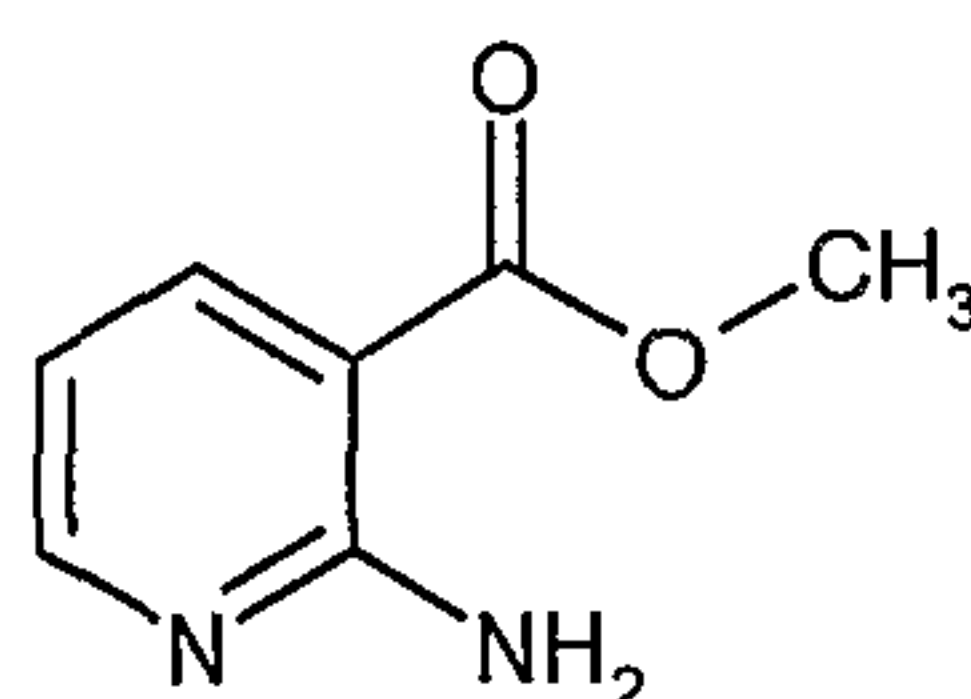


15 A mixture of 1-(4-aminomethyl-pyridin-2-yl)-3-methyl-urea (3.8 g, 21.1 mmol) and 2-chloro-nicotinic acid methyl ester [Mann et al. *J. Chem. Soc.*; 1952; 2057, 2060] (1.78 g, 10.4 mmol) was heated for 1 hour at 120 °C. The crude product was purified by chromatography on silica gel (Gradient elution: 100% CH₂Cl₂ to 93% CH₂Cl₂/ 7% MeOH) to give 2-[[2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino]-nicotinic acid methyl ester (2.06 g); Mp. 145-146 °C.

20

Example 4.1

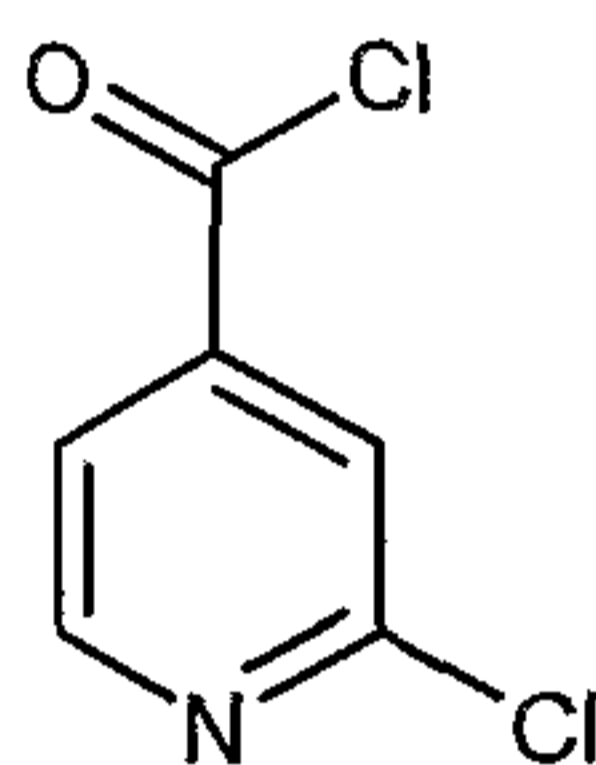
Preparation of 2-amino-nicotinic acid methyl ester



A stirred suspension of 2-amino-nicotinic acid (12.15 g, 87.95 mmol) in a mixture of MeOH (175 mL) and THF (500 mL), under nitrogen at room temperature, was added a solution of trimethylsilyldiazomethane (2M in hexane, 50 mL, 99.5 mmol) dropwise. After completion of the reaction the
5 volatiles were removed *in vacuo* and the crude product triturated with disisopropyl ether, filtered and dried to give 2-amino-nicotinic acid methyl ester (10.44 g) as a yellow solid.

Example 4.2

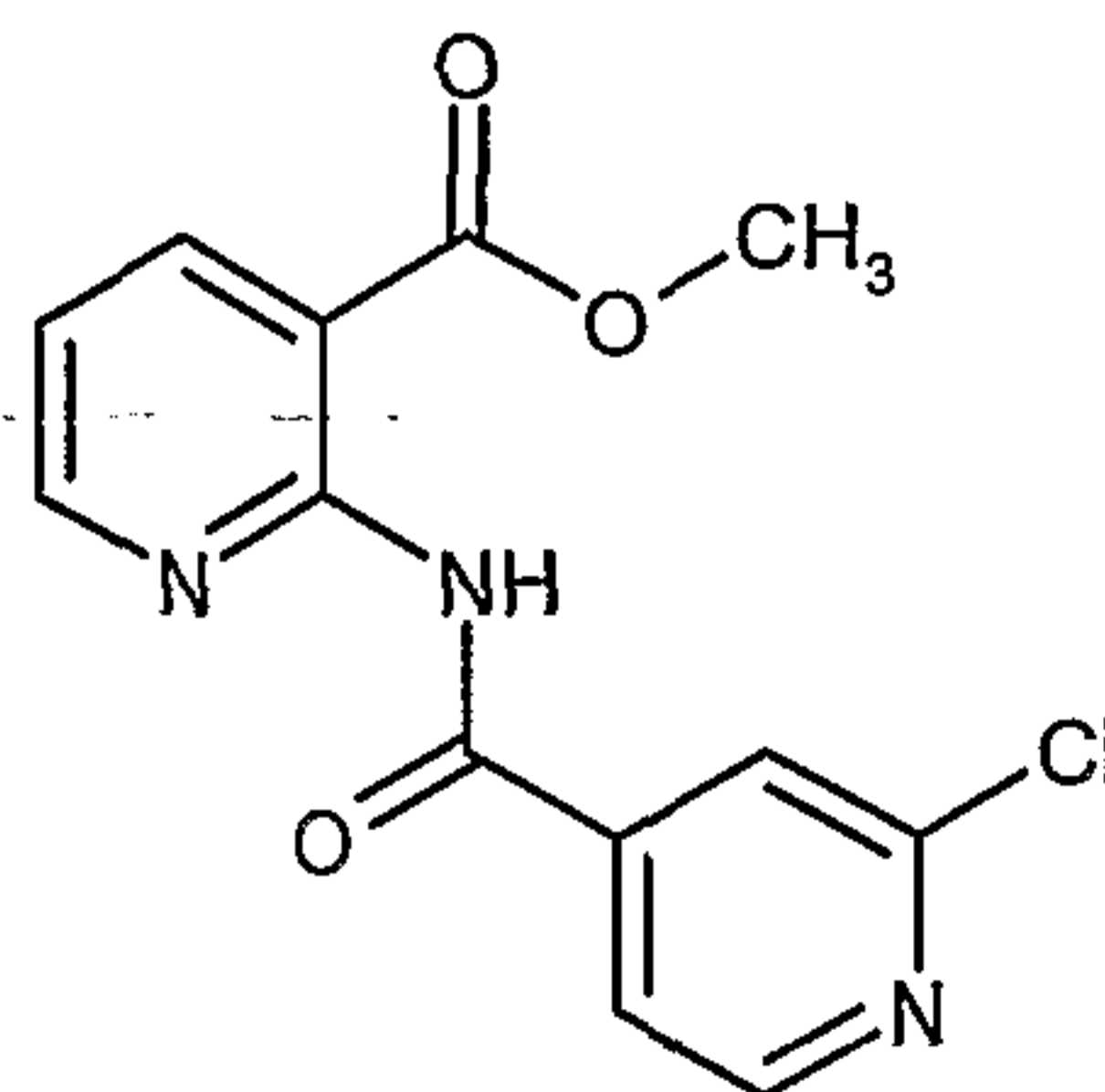
10 Preparation of 2-chloro-isonicotinoyl chloride



A mixture of 2-chloro-isonicotinic acid (15 g, 95.2 mmol) and thionyl chloride (90 mL) was heated at 100 °C. After completion of the reaction the mixture
15 was concentrated *in vacuo*. Residual thionyl chloride was removed by azeotropic distillation with toluene, to give 2-chloro-isonicotinoyl chloride (15.33 g).

Example 4.3

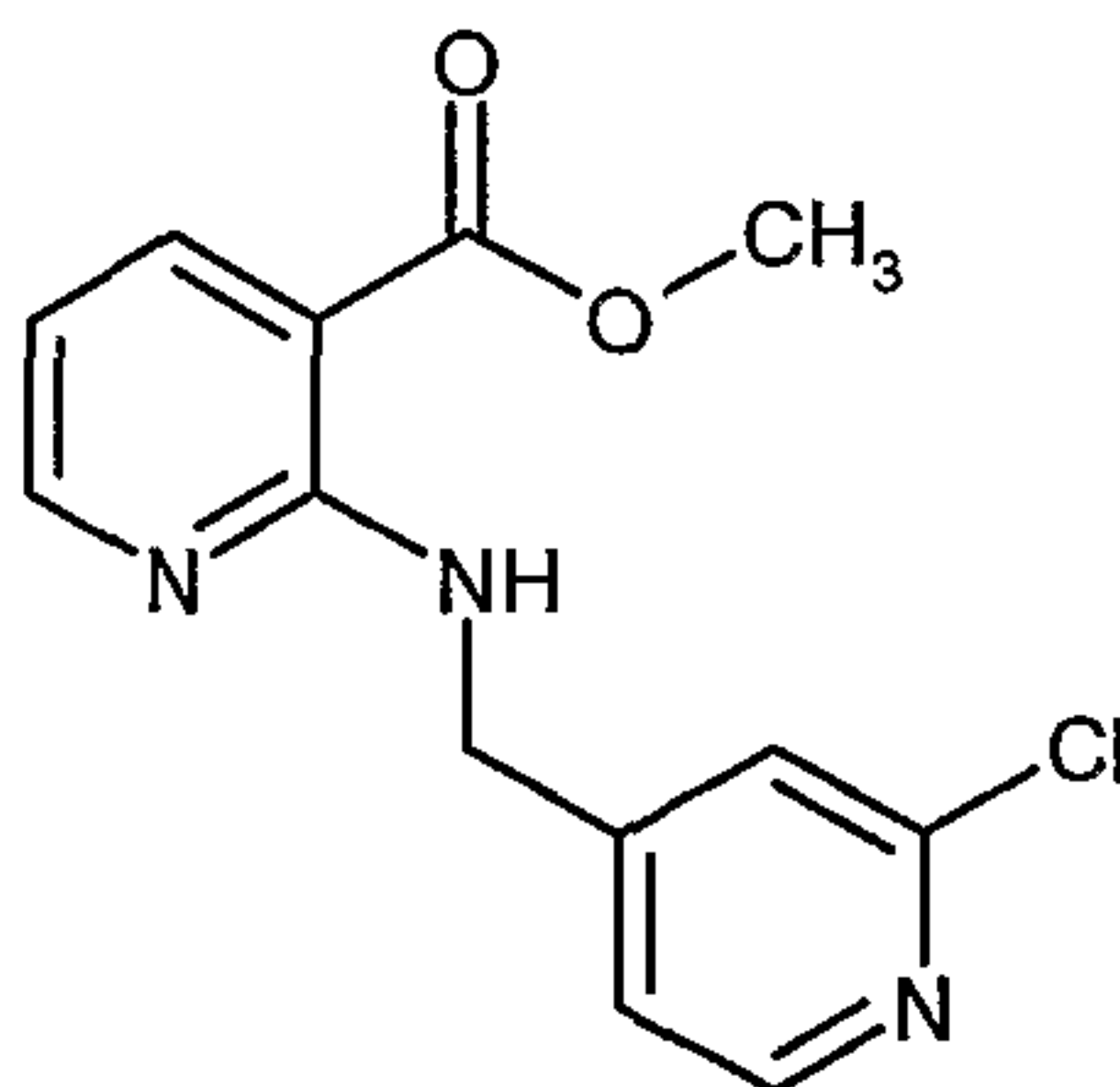
20 Preparation of 2-[(2-chloro-pyridine-4-carbonyl)-amino]-nicotinic acid methyl ester



A stirred and chilled (0 °C) mixture of 2-amino-nicotinic acid methyl ester (11 g, 72.3 mmol) in dichloromethane was treated sequentially with triethylamine (11 mL, 79.5 mmol) and a solution of 2-chloro-isonicotinoyl chloride (12.73 g, 72.3 mmol) in dichloromethane, such that the total volume of solvent was 80 mL. The reaction was warmed to room temperature and on completion of the reaction was quenched by addition of water. The aqueous phase was separated and extracted with EtOAc. The combined organic phases were washed with brine, dried and concentrated *in vacuo*. The residue was suspended in hot hexane, filtered while hot and the resulting solid recrystallised from EtOH, to give 2-[(2-chloro-pyridine-4-carbonyl)-amino]-nicotinic acid methyl ester (12.76 g); ¹H-NMR (300 MHz, d₆-DMSO) 11.47 (1H, s), 8.62-8.67 (2 H, m), 8.20 (1H, unresolved dd), 7.99 (1H, s), 7.89 (1H, unresolved dd), 7.43 (1H, dd), 3.72 (3H, s).

15 Example 4.4

Preparation of 2-[(2-chloro-pyridin-4-ylmethyl)-amino]-nicotinic acid methyl ester

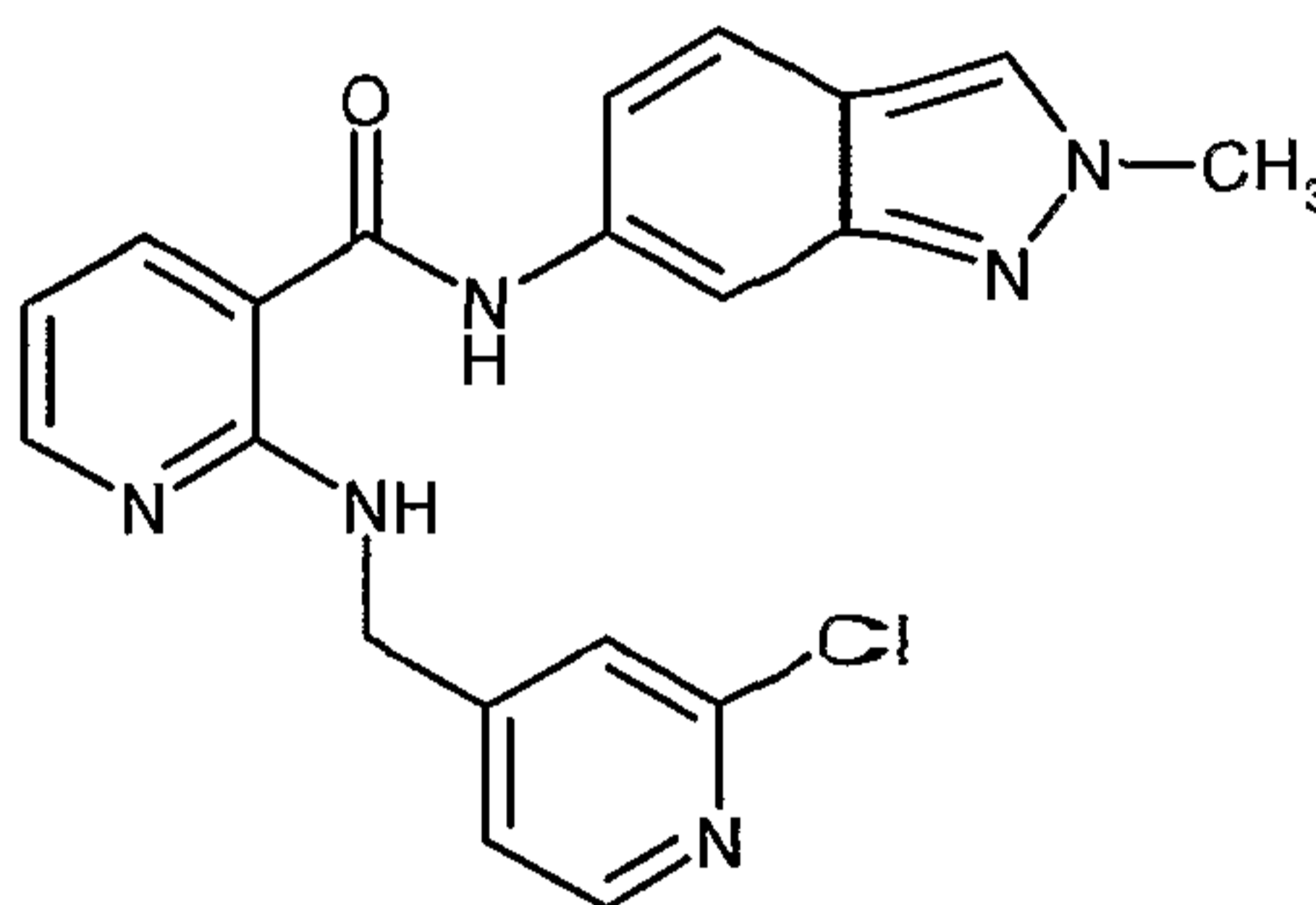


20 A stirred solution of 2-[(2-chloro-pyridine-4-carbonyl)-amino]-nicotinic acid methyl ester (4 g, 13.72 mmol) in dry THF (60 mL), under nitrogen, was treated with borane-dimethyl sulphide complex (2M solution in THF, 34 mL, 68.6 mmol). On completion of the reaction the mixture was carefully poured into MeOH and the resulting mixture heated at reflux for 30 minutes. The volatiles were removed *in vacuo* and the residue partitioned between dilute aqueous sodium hydrogencarbonate solution and dichloromethane. The

aqueous layer was extracted with dichloromethane and the combined organic layers washed with brine, dried and concentrated *in vacuo*. Purification was achieved by chromatography on Isolute® flash silica gel (Separtis) to give 2-
 5 [(2-chloro-pyridin-4-ylmethyl)-amino]-nicotinic acid methyl ester (0.76 g); ¹H-NMR (300 MHz, d₆-DMSO) 8.47 (1H, t), 8.30 (1H, d), 8.23 (1H, unresolved dd), 8.13 (1H, unresolved dd), 7.38 (1H, s), 7.30 (1H, d), 6.68 (1H, dd), 4.73 (2H, d), 3.85 (3H, s).

Example 4.4

10 Preparation of 2-[(2-chloro-pyridin-4-ylmethyl)-amino]-N-(2-methyl-2H-indazol-6-yl)-nicotinamide

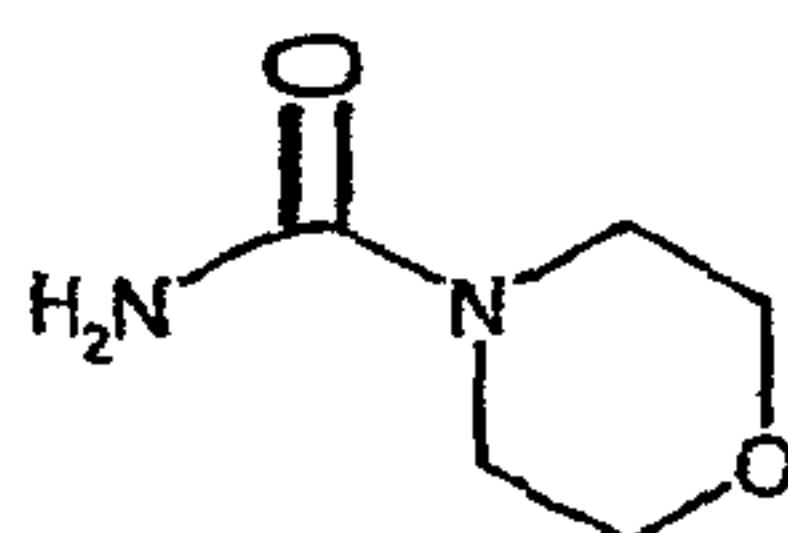


To a stirred and chilled (0 °C) suspension of 2-methyl-2H-indazol-6-ylamine
 15 (1.52 g) in DCE (6 mL), under nitrogen, was added trimethylaluminium (2M solution in toluene, 5 mL, 9.37 mmol). This mixture was added dropwise to a stirred and chilled (0 °C) solution of 2-[(2-chloro-pyridin-4-ylmethyl)-amino]-nicotinic acid methyl ester (1.45 g, 5.21 mmol) in DCE (14.7 mL). The mixture was heated at 100 °C for 2 hours before cooling to room temperature and
 20 quenching by pouring into aqueous sodium-potassium tartrate solution. The mixture was extracted with EtOAc and the combined organic layers washed successively with dilute aqueous citric acid solution, dilute aqueous sodium hydrogen carbonate solution and brine, dried and concentrated *in vacuo* to give
 25 2-[(2-chloro-pyridin-4-ylmethyl)-amino]-N-(2-methyl-2H-indazol-6-yl)-nicotinamide (1.58 g); ¹H-NMR (300 MHz, d₆-DMSO) 10.26 (1H, s), 8.40 (1H, t), 8.28 (1H, d), 8.25 (1H, s), 8.06-8.12 (3H, m), 7.62 (1H, d), 7.35 (1H, s), 7.30

(1H, unresolved dd), 7.27 (1H, unresolved dd), 6.68 (1H, dd), 4.67 (2H, d), 4.10 (3H, s).

Example 5.0

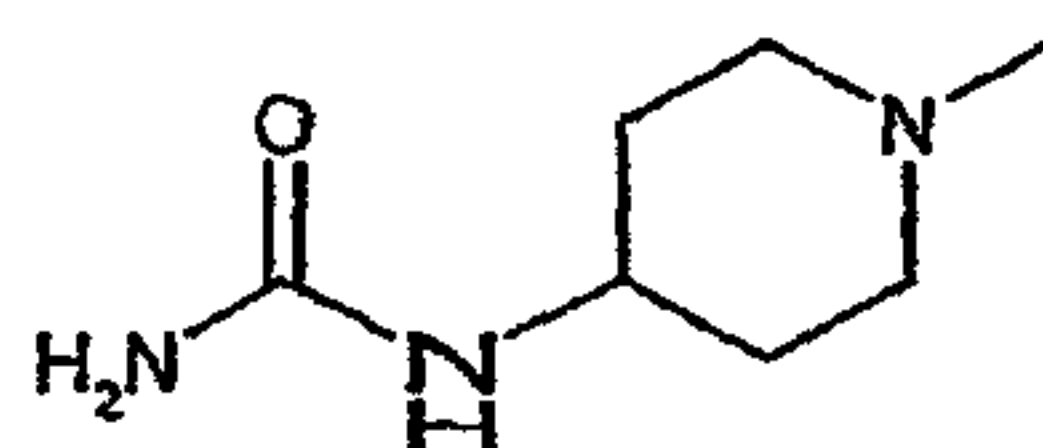
5 Preparation of morpholine-4-carboxylic acid amide



To a stirred solution of morpholine (1.3 mL, 15 mmol) in isopropanol (30 mL) at rt was added trimethylsilylisocyanate (2.8 mL, 21 mmol) and the resulting solution stirred overnight before the volatiles were removed in vacuo to give morpholine-4-carboxylic acid amide (2.0 g, quant.) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 6.00 (2H, s), 3.51-3.54 (4H, s), 3.23-3.26 (4H, s).

15 Example 5.1

Preparation of (1-methyl-piperidin-4-yl)-urea



(1-methyl-piperidin-4-yl)-urea was prepared from 1-methyl-piperidin-4-ylamine and trimethylsilylisocyanate, in analogy to Example 5.0; ¹H-NMR (300 MHz, d₆-DMSO) 5.86 (1H, d), 5.32 (2H, s), 3.21-3.38 (1H, m), 2.58-2.67 (2H, m), 2.11 (3H, s), 1.88-1.98 (2H, m), 1.65-1.72 (2H, m), 1.22-1.35 (2H, m).

The following examples detail the biological activity and use of the compounds of the invention. The scope of the claimed compounds should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

KDR Kinase Inhibition

Kinase activity was measured with a GST-kinase domain fusion construct of
5 the KDR kinase according to the following protocol to obtain concentration
response curves. Components were added into a microtiterplate in the
following sequence: 10 μ l of inhibitor in threefold final concentration [3%
DMSO in buffer (40 mM TrisCl pH 7.5; 1 mM DTT, 1 mM $MnCl_2$, 10 mM $MgCl_2$, 2.5
Promille Polyethyleneglycol 20000)] and 10 μ l of substrate mixture [24 μ M ATP,
10 24 μ g/ml poly(Glu₄Tyr) in buffer, specific activity approx. 500 cpm/pmol ³²P-
 γ ATP]. Reaction was started by adding 10 μ l of enzyme preparation diluted
appropriately in buffer that contains 10 μ M vanadate. After incubation for
exactly 10 min the reaction was stopped by adding of 10 μ l stop solution
(250mM EDTA). 10 μ l of the reaction mixture were transferred to
15 phosphocellulose filters. The filters were washed in 0.1% phosphoric acid,
dried before meltilex scintillator was applied (Wallac, Perkin-Elmer) and the
radioactivity was counted.

VEGFR-3 Autophosphorylation

20 MVECs (1,5x10⁶/well) of a low passage number were plated on collagen-G
coated 48 well plates in EBM complete medium (including EGM-2, BD-
Clonotech). 5h later, medium was exchanged for EBM-2 without EGM-2 but
containing 0.2% BSA (EBM meager). 12 h later medium was removed, 250 μ l
25 EBM-2 meager and the respective compound dilutions were added in 50 μ l EBM-
2 meager. Solutions were carefully mixed and left for 5 min at 4°C before the
addition of 200 μ l EBM-2 meager containing VEGF-C (final concentration in the
assay is 5 nM; Reliatech, Braunschweig). The solution was then carefully mixed
and incubated for 15 min at room temperature. The medium was removed and
30 cells were washed twice with cold PBS/2mM vanadate. Cells were then lysed
with 100 μ l Duschl buffer [50mM Hepes pH 7,2; 150 mM NaCl; 1 mM $MgCl_2$; 1,5%

Triton* X-100; 10 mM Na-Pyrophosphate; 100 mM Na-Fluoride; 10% glycerol + (freshly added before the experiment) 2 mM Orthovanadate and 1 tablet per 50 ml Complete (Roche # 1836145)]

5 For the ELISA, Fluoronic MaxiSorp - MTP plates (# 3204006 Zinser)- were coated overnight at 4°C with Flt-4 antibody (Flt-4 (C-20) # sc-321 Santa Cruz); 1µg/ml in coating buffer: Na₂CO₃ pH 9,6 100µl/well). After 3x washing with washing buffer (0,1% Tween* 20 in Na₂HPO₄ pH 7.4) the wells were incubated with 250µl blocking buffer (Roti Block 1/10 from Roth, Karlsruhe for 1 h at
10 room temperature). 3x Washing with washing buffer was followed by addition of cell lysates and incubation over night at 4°C. Then wells were washed 3x, anti-phosphotyrosine antibody coupled to HRP(16-105; UPSTATE; dilution 1/20000 in TBST+3% Top Block # 37766, Fluka) was added and incubated overnight at 4°C. Washing with washing buffer (6x) preceded the addition of
15 BM chemoluminescence ELISA reagent # 1582950 (Roche) and measurement of luminescence.

Cytochrome P450 Inhibition

The Cytochrome P450 isoenzyme inhibition was performed according to the
20 publication of Crespi et al. (Anal. Biochem., 1997, 248, 188-190) with use of the baculovirus/insect cell-expressed, human Cytochrome P 450 isoenzymes (2C9 and 2C19).

Selected results are presented in the following table :

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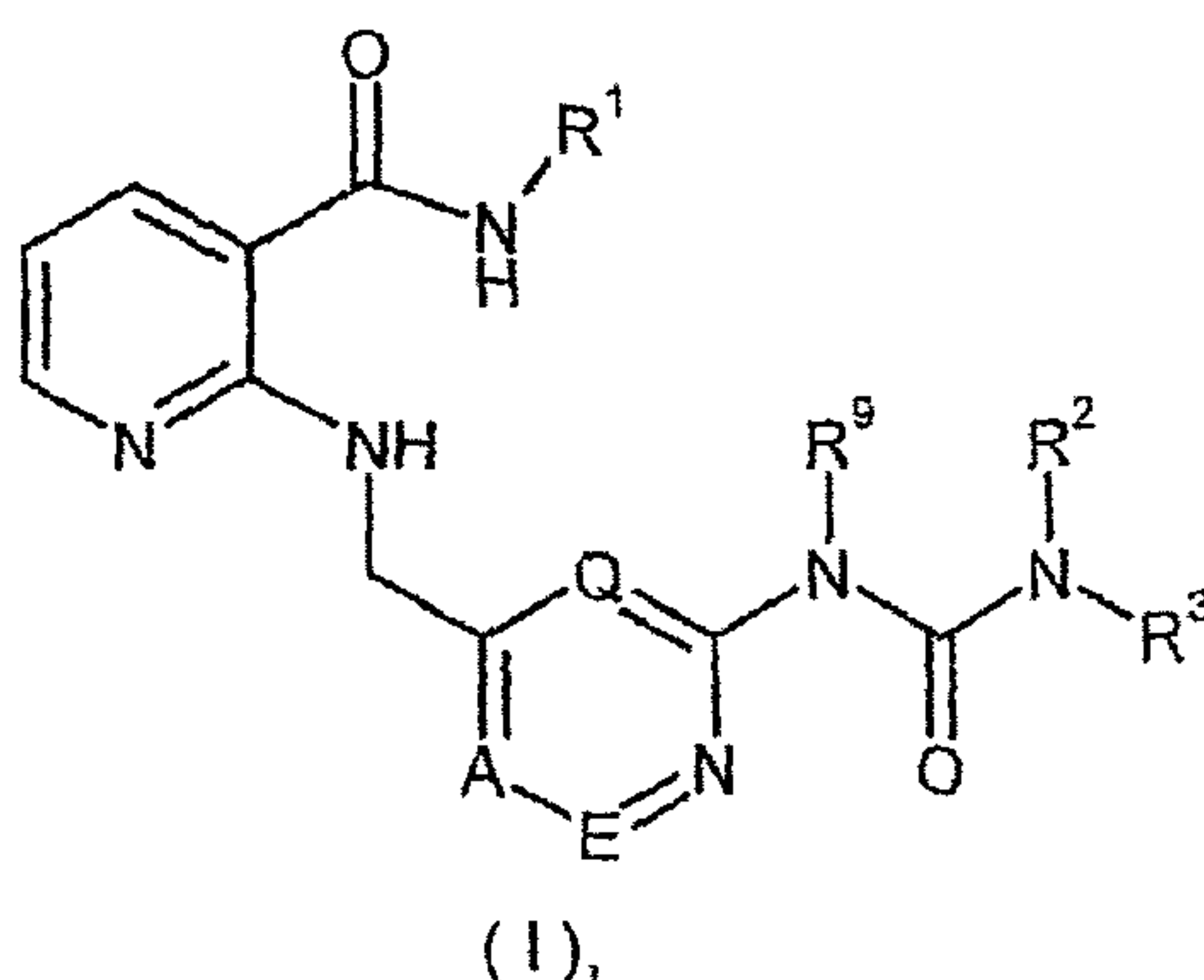
* TRADE-MARK

Example	IC50 KDR-Kinase (VEGFR-2) (nM)	IC50 CYP 2C9 (μ M)	IC50 CYP 2C19 (μ M)
3.30 from WO 04/13102	10	0.9	1.7
3.40 from WO 04/13102	40	1.1	2.3
3.41 from WO 04/13102	27	5.7	1.5
3.36 from WO 04/13102	98	1.2	9.0
1.0	10	11.7	>30.0
2.0	29	>30.0	>30.0

The advantages of the compounds of the invention compared to known compounds can be readily demonstrated by the above studies.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound of formula (I):



wherein:

A, E and Q independently of one another, are CH or N, wherein a maximum of two nitrogen atoms are contained in the ring;

R¹ is aryl or heteroaryl, which is optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₃-C₆-cycloalkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, aralkyloxy, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, cyano-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, wherein C₁-C₁₂-alkyl may be substituted with -OR⁵ or -NR⁷R⁸;

R², R³ and R⁹ independently of one another, are hydrogen or C₁-C₁₂ alkyl optionally substituted with halogen, -OR⁵, or C₁-C₁₂-alkoxy; or

R⁹ is hydrogen, and

R² and R³ together with the nitrogen atom to which they are attached form a 3-8 membered heterocycloalkyl ring, which optionally contains a further heteroatom and which is optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶, or -CO₂R⁶, wherein C₁-C₁₂ alkyl is optionally substituted with a group -OR⁵; or

R³ is hydrogen or C₁-C₁₂-alkyl, wherein C₁-C₁₂ alkyl is optionally substituted with a group -OR⁵, and

- R^2 and R^9 together with the two nitrogen atoms to which they are attached form a 5-7 membered ring, which is optionally further substituted in one or more places in the same way or differently with halogen, C_1 - C_{12} -alkyl, C_1 - C_{12} -alkoxy, halo- C_1 - C_6 -alkyl, or =O, wherein C_1 - C_{12} alkyl is optionally substituted with a group $-OR^5$;
- R^4 is C_1 - C_{12} -alkyl, C_3 - C_8 -cycloalkyl, aryl or heteroaryl;
- R^5 is hydrogen, C_1 - C_{12} -alkyl, C_3 - C_8 -cycloalkyl or halo- C_1 - C_6 -alkyl;
- R^6 is hydrogen, C_1 - C_{12} -alkyl, C_3 - C_8 -cycloalkyl, halo- C_1 - C_6 -alkyl, aryl, or $-NR^7R^8$; and
- R^7 and R^8 independently of one another, are hydrogen, $-SO_2R^6$, $-COR^6$, aryl, C_3 - C_8 -cycloalkyl, C_1 - C_{12} -alkyl, halo- C_1 - C_{12} -alkyl, or C_1 - C_{12} -alkoxy, wherein C_1 - C_{12} -alkyl is optionally substituted with $-OR^5$ or $-N(CH_3)_2$, or R^7 and R^8 provide a 3-8 membered cycloalkyl ring, which optionally contains a further heteroatom, and is optionally substituted in one or more places in the same way or differently with halogen, cyano, C_1 - C_{12} -alkyl, C_1 - C_{12} -alkoxy, halo- C_1 - C_6 -alkyl, =O, $-OR^5$, COR^6 , $-SR^4$, $-SOR^4$ or $-SO_2R^6$;

or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof.

2. A compound as claimed in claim 1, wherein A, E, and Q each are CH.
3. A compound as claimed in claim 1 or 2, wherein R^1 is phenyl, isoquinolyl, quinolinyl or indazolyl optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C_1 - C_{12} -alkyl, C_3 - C_6 -cycloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, aralkyloxy, C_1 - C_{12} -alkoxy, halo- C_1 - C_6 -alkyl, cyano- C_1 - C_6 -alkyl, =O, $-SO_2R^6$, $-OR^5$, $-SOR^4$, $-COR^6$, $-CO_2R^6$ or $-NR^7R^8$, wherein C_1 - C_{12} -alkyl may be substituted with $-OR^5$ or $-NR^7R^8$.
4. A compound as claimed in claim 1 or 2, wherein R^1 is indazolyl substituted in one or more places in the same way or differently with halogen, hydroxy,

C₁-C₁₂-alkyl, C₃-C₆-cycloalkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, aralkyloxy, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, cyano-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, wherein C₁-C₁₂-alkyl may be substituted with -OR⁵ or -NR⁷R⁸.

5. A compound as claimed in claim 1 or 2, wherein R¹ is indazolyl substituted with C₁-C₁₂-alkyl, optionally having a halogen atom substituent.
6. A compound as claimed in 1 or 2, wherein R¹ is indazolyl substituted with -CH₃.
7. A compound as claimed in claim 1 or 2, wherein R¹ is 2-methyl-indazolyl.
8. A compound as claimed in any one of claims 1 to 7, wherein R², R³ and R⁹ independently of one another, are hydrogen or C₁-C₁₂ alkyl optionally substituted with halogen, -OR⁵ or C₁-C₁₂-alkoxy.
9. A compound as claimed in claim 8, wherein R², R³ and R⁹ independently of one another, are hydrogen or C₁-C₁₂ alkyl.
10. A compound as claimed in claim 8, wherein R² and R³ independently of one another, are hydrogen or -CH₃ and R⁹ is hydrogen.
11. A compound as claimed in any one of claims 1 to 7, wherein R⁹ is hydrogen and R² and R³ together with the nitrogen atom to which they are attached form a 3-8 membered heterocycloalkyl ring, which optionally contains a further heteroatom and which is optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶, or -CO₂R⁶, wherein C₁-C₁₂ alkyl is optionally substituted with a group -OR⁵.
12. A compound as claimed in claim 11, wherein R⁹ is hydrogen and R² and R³ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl ring, which optionally contains at least one further

heteroatom and which is optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶, or -CO₂R⁶, wherein C₁-C₁₂ alkyl is optionally substituted with a group -OR⁵.

13. A compound as claimed in any one of claims 1 to 7, wherein R³ is hydrogen or C₁-C₁₂-alkyl, wherein C₁-C₁₂-alkyl is optionally substituted with a -OR⁵ group and R² and R⁹ together with the two nitrogen atoms to which they are attached form a 5-7 membered ring, which is optionally further substituted in one or more places in the same way or differently with halogen, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, or =O, wherein C₁-C₁₂ alkyl is optionally substituted with a group -OR⁵.

14. A compound as claimed in claim 13, wherein R³ is hydrogen or -CH₃ and R² and R⁹ together with the two nitrogen atoms to which they are attached form a 5-7 membered saturated ring, which is optionally further substituted in one or more places in the same way or differently with halogen, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, or =O, wherein C₁-C₁₂ alkyl is optionally substituted with a group -OR⁵.

15. A compound as claimed in claim 13, wherein R³ is hydrogen and R² and R⁹ together with the two nitrogen atoms to which they are attached form a 5 membered saturated ring, which is optionally further substituted in one or more places in the same way or differently with halogen, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, or =O, wherein C₁-C₁₂ alkyl is optionally substituted with a group -OR⁵.

16. A compound as claimed in any one of claims 1 to 15, wherein R⁴ is C₁-C₁₂-alkyl.

17. A compound as claimed in any one of claims 1 to 15, wherein R⁴ is -CH₃.

18. A compound as claimed in any one of claims 1 to 17, wherein R⁵ is -CH₃ or hydrogen.
19. A compound as claimed in any one of claims 1 to 17, wherein R⁵ is hydrogen.
20. A compound as claimed in any one of claims 1 to 19, wherein R⁶ is C₁-C₁₂-alkyl or -NR⁷R⁸.
21. A compound as claimed in any one of claims 1 to 19, wherein R⁶ is C₁-C₁₂-alkyl.
22. A compound as claimed in any one of claims 1 to 19, wherein R⁶ is -CH₃.
23. A compound as claimed in any one of claims 1 to 22, wherein R⁷ and R⁸ independently of one another, are hydrogen, -COR⁶, -SO₂R⁶, or C₁-C₁₂-alkyl.
24. A compound as claimed in any one of claims 1 to 22, wherein R⁷ and R⁸ independently of one another, are hydrogen or -CH₃.
25. A compound as claimed in claim 1, which is:
 N-(2-methyl-2H-indazol-6-yl)-2-[[2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino]-nicotinamide;
 2-[[2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino]-N-(3-trifluoromethyl-phenyl)-nicotinamide;
 N-(1-methyl-1H-indazol-6-yl)-2-[[2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino]-nicotinamide;
 N-isoquinolin-3-yl-2-[[2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino]-nicotinamide;
 N-(1-methyl-1H-indazol-5-yl)-2-[[2-(3-methyl-ureido)-pyridin-4-ylmethyl]-amino]-nicotinamide;

morpholine-4-carboxylic acid (4-{{3-(2-methyl-2H-indazol-6-ylcarbamoyl)-pyridin-2-ylamino}-methyl}-pyridin-2-yl)-amide;

2-{{2-(3,3-dimethyl-ureido)-pyridin-4-ylmethyl}-amino}-N-(2-methyl-2H-indazol-6-yl)-nicotinamide;

N-(2-methyl-2H-indazol-6-yl)-2-{{2-[3-(1-methyl-piperidin-4-yl)-ureido]-pyridin-4-ylmethyl}-amino)-nicotinamide; or

N-(2-methyl-2H-indazol-6-yl)-2-{{2-(2-oxo-imidazolidin-1-yl)-pyridin-4-ylmethyl}-amino}-nicotinamide;

or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof.

26. A pharmaceutical composition comprising at least one compound of formula (I) as defined in any one of claims 1 to 25, and at least one pharmaceutically acceptable carrier.

27. A pharmaceutical composition according to claim 26 for use in the prevention or treatment of a disease associated with persistent angiogenesis, a disease associated with excessive lymphangiogenesis, or a combination thereof.

28. A pharmaceutical composition according to claim 26 for use in the prevention or treatment of tumor- or metastases-growth; psoriasis; Kaposi's sarcoma; restenosis; stent-induced restenosis; Crohn's disease; Hodgkin's disease; leukemia; arthritis; endometriosis; eye disease; corneal transplants; renal disease; fibrotic disease; mesangial cell proliferative disease; arteriosclerosis; injuries to the nerve tissue; for inhibiting the reocclusion of vessels after balloon catheter treatment; in vascular prosthetics; after mechanical devices are used to keep vessels open; as an immunosuppressive agent for supporting scar-free healing; senile keratosis; contact dermatitis; or asthma.

29. Use of a compound of general formula (I) as defined in any one of claims 1 to 25 in the manufacture of a medicament for the prevention or treatment of tumor or metastasis growth, psoriasis, Karposi's sarcoma, restenosis, stent-induced restenosis, Crohn's disease, Hodgkin's disease, leukemia, arthritis,

endometriosis, eye disease, corneal transplants, renal disease, fibrotic disease, mesangial cell proliferative disease, arteriosclerosis, injuries to the nerve tissue, for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics, after mechanical devices are used to keep vessels open, as an immunosuppressive agent for supporting scar-free healing, senile keratosis, contact dermatitis, or asthma.

30. A pharmaceutical composition according to claim 28, or a use according to claim 29, wherein the arthritis is rheumatoid arthritis, hemangioma, or angiofibroma.

31. A pharmaceutical composition according to claim 28, or a use according to claim 29, wherein the eye disease is diabetic retinopathy or neovascular glaucoma.

32. A pharmaceutical composition according to claim 28, or a use according to claim 29, wherein the renal disease is glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndrome, transplant rejections or glomerulopathy.

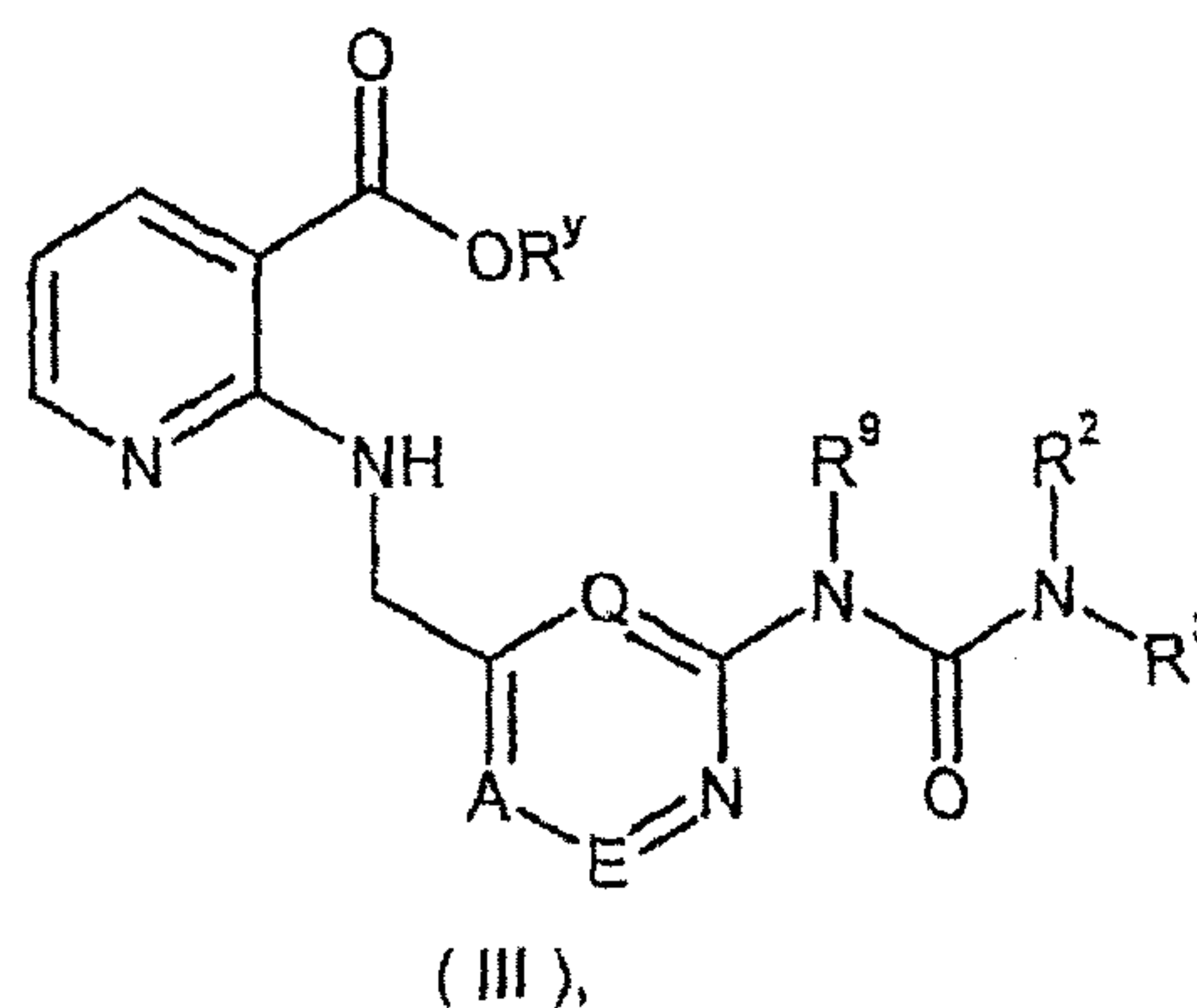
33. A pharmaceutical composition according to claim 28, or a use according to claim 29, wherein the fibrotic disease is cirrhosis of the liver.

34. A pharmaceutical composition according to claim 26 for use as a VEGF receptor kinase 3-inhibitor of lymphangiogenesis.

35. A compound of formula (I) according to any one of claims 1 to 25 for use in the preparation of a pharmaceutical product for the prevention or treatment of a disease for which an inhibition of angiogenesis and/or lymphangiogenesis and/or a VEGF receptor kinase is beneficial.

36. A compound of formula (I) according to any one of claims 1 to 25 for use as an inhibitor of a tyrosine kinase which is VEGFR-1 or VEGFR-2.

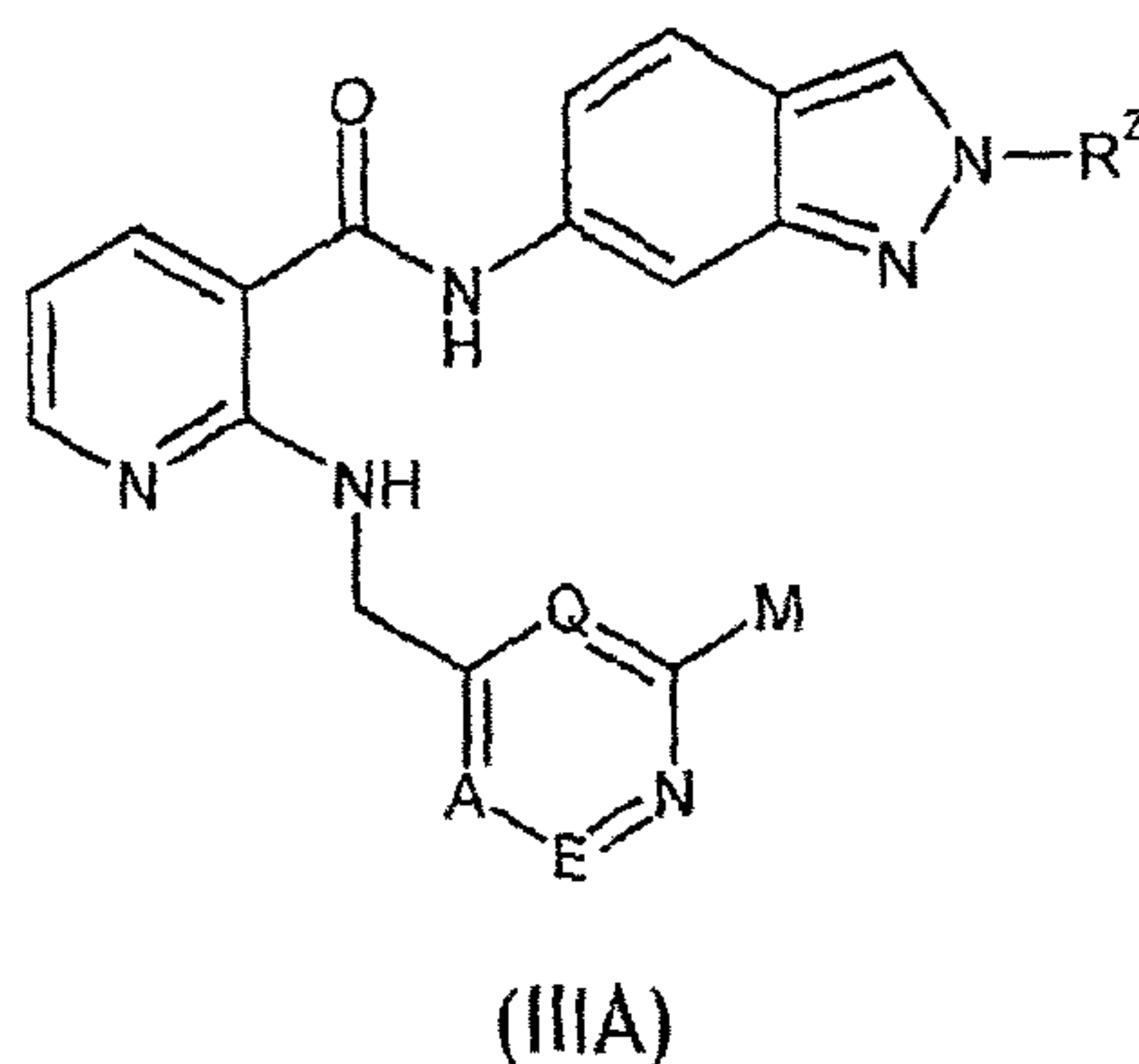
37. A compound of general formula (III):



in which A, E, Q, R², R³ and R⁹ are as defined in any one of claims 1 to 25, and R^y is H or C₁-C₆-alkyl, for use as an intermediate for the preparation of a compound of formula (I) as defined in any one of claims 1 to 25.

38. A compound as claimed in claim 37, wherein R^y is H or C₁-C₂-alkyl.

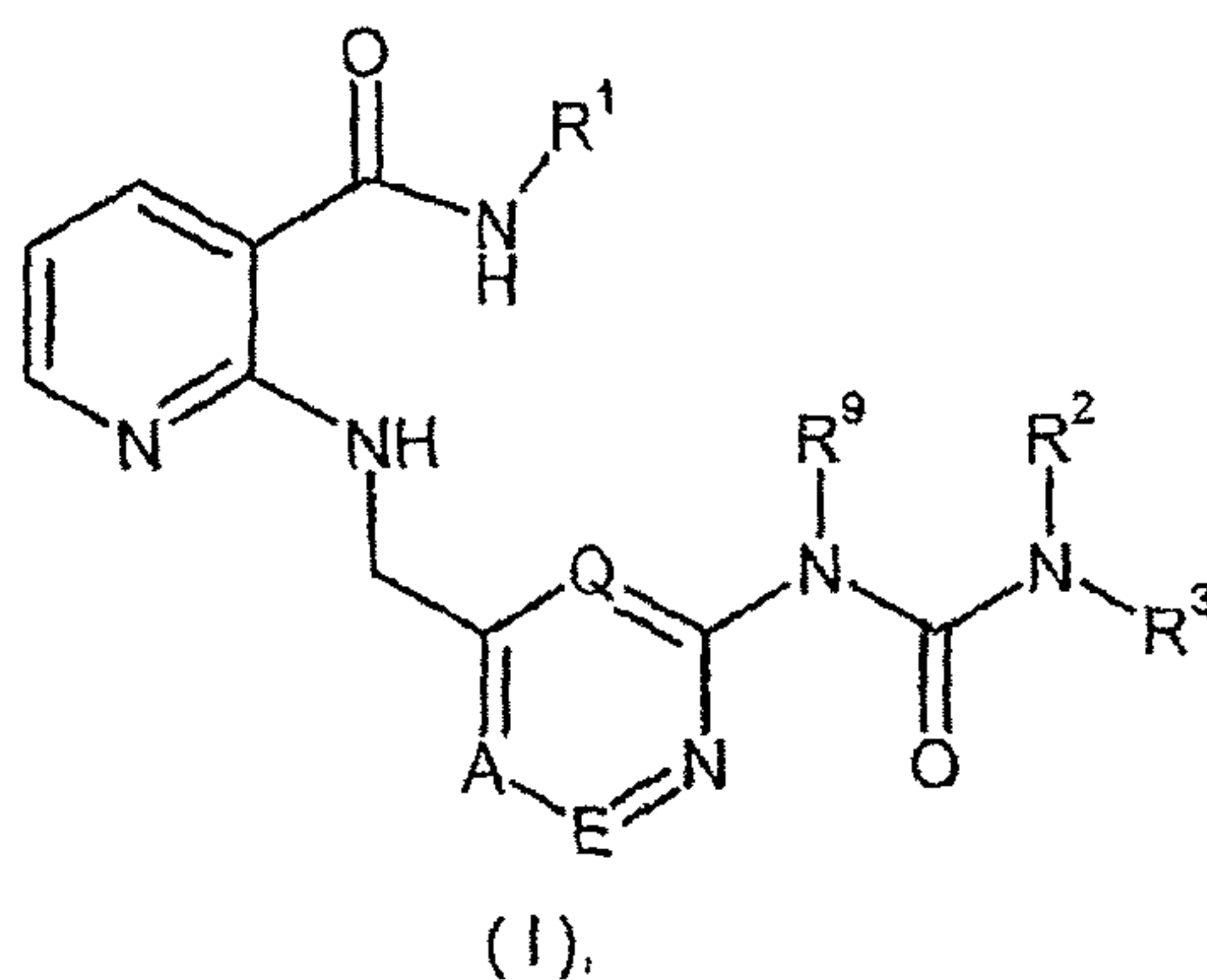
39. A compound of general formula (IIIA):



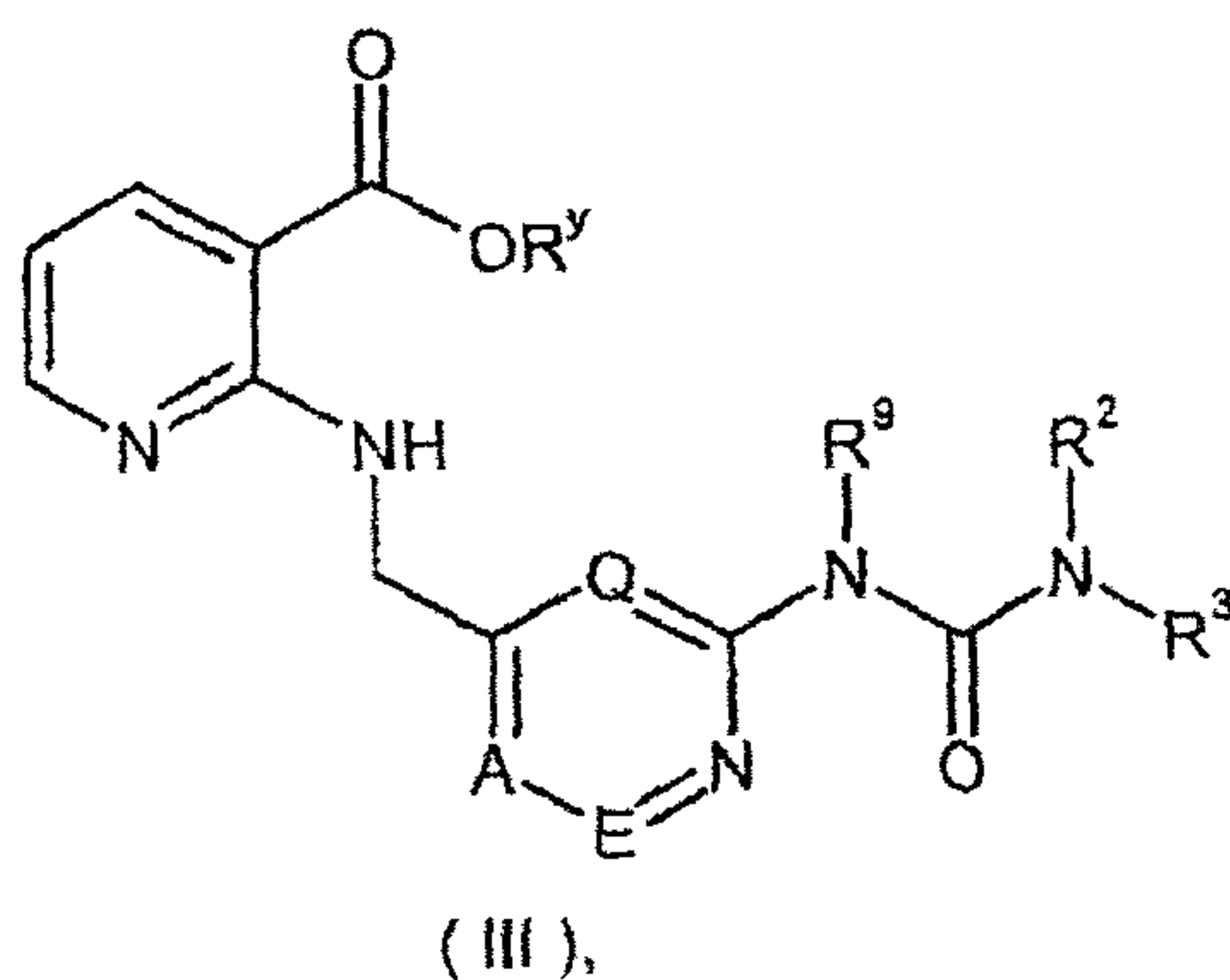
in which A, E, Q and R¹ are as defined in any one of claims 1 to 25, R^z is C₁-C₁₂-alkyl, and M is halogen, for use as an intermediate for the preparation of a compound of formula (I) as defined in any one of claims 1 to 25.

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40. A process for the preparation of a compound of formula (I):

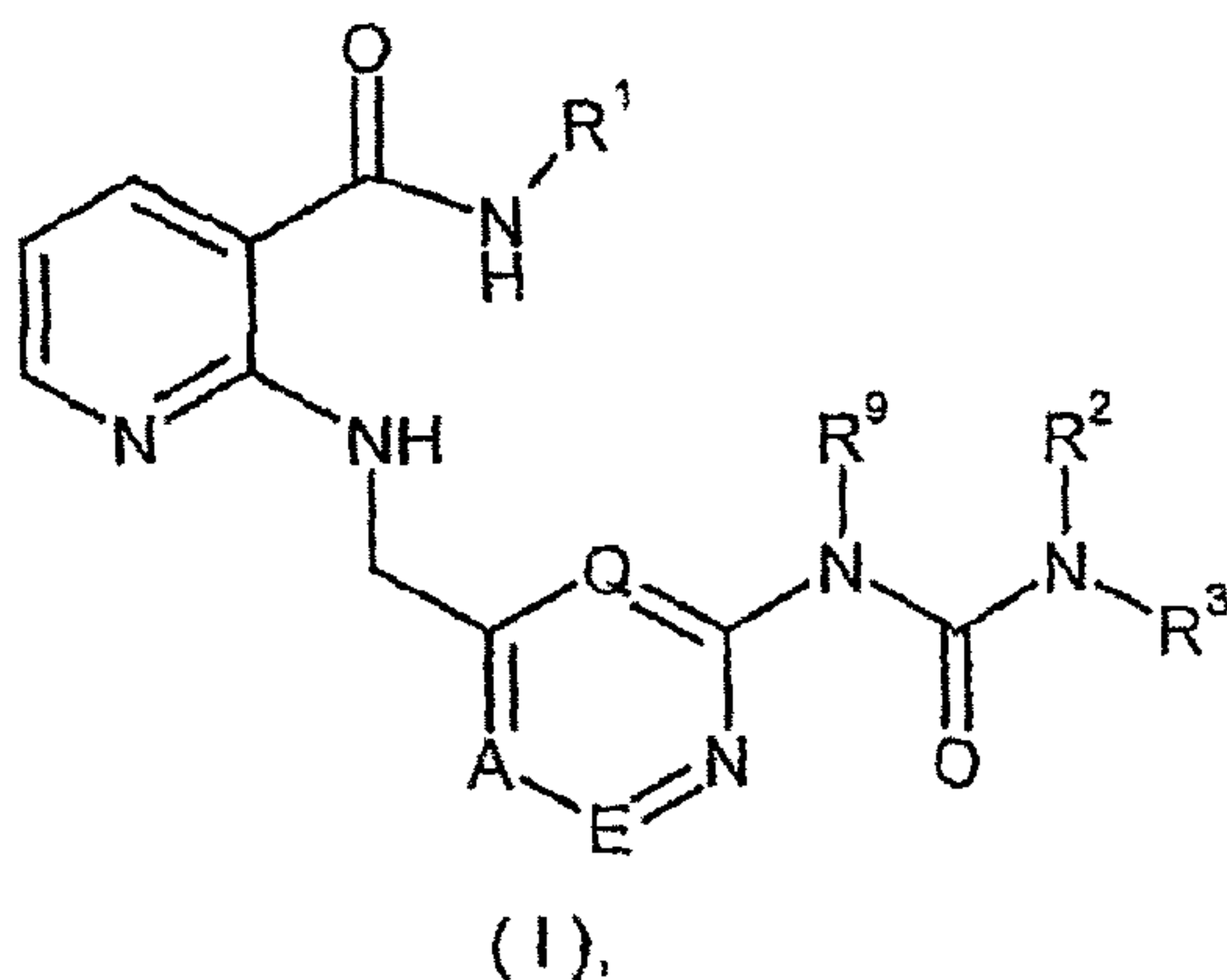


wherein R^1 , R^2 , R^3 , R^9 , A, E and Q are as defined in any one of claims 1 to 25, in which a compound of formula (III):



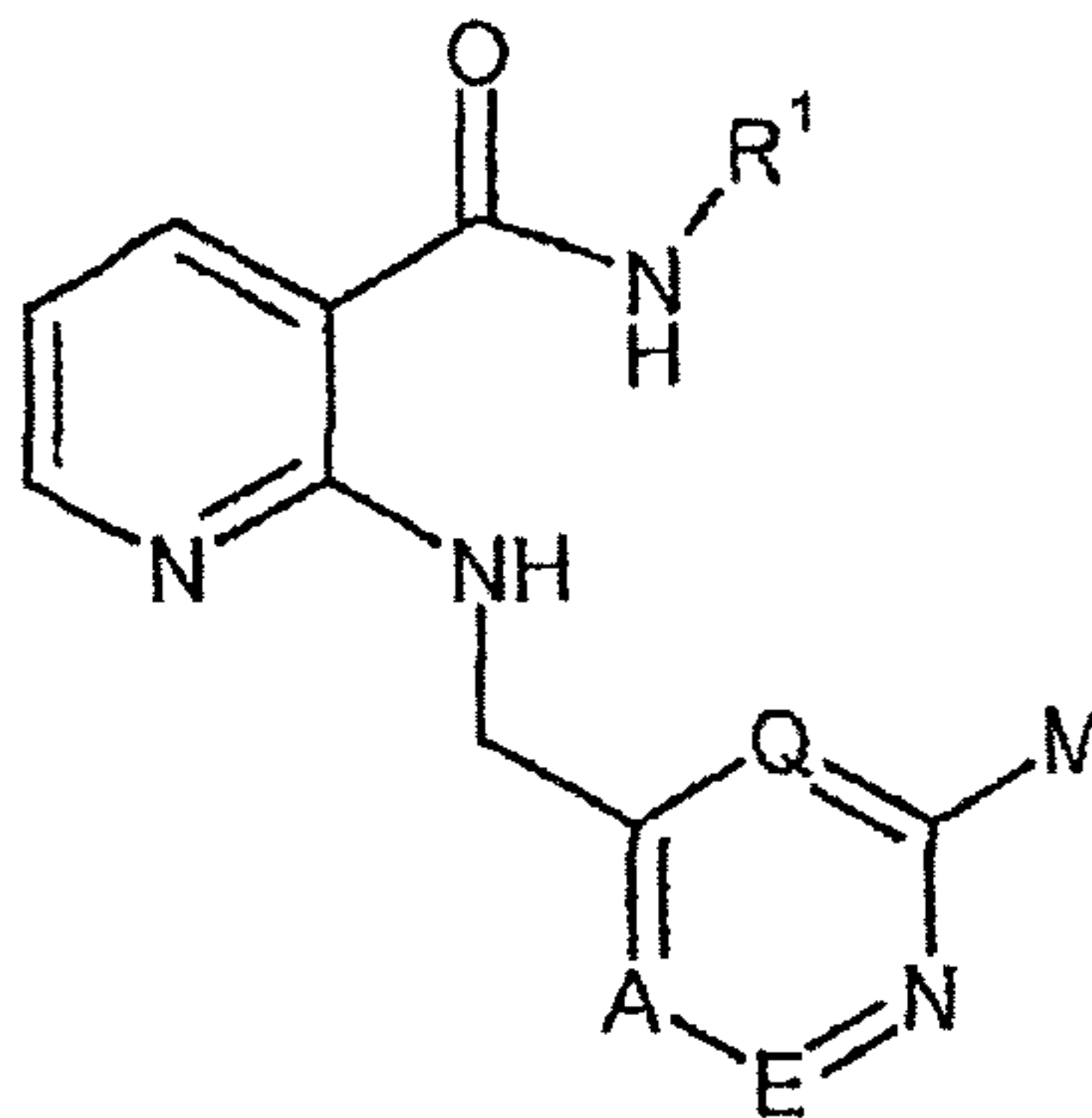
as defined in claim 37 or 38, is reacted with an amine of formula R^1NH_2 in which R^1 is as defined in any one of claims 1 to 25.

41. A process for the preparation of a compound of formula (I):



wherein R^1 , R^2 , R^3 , R^9 , A, E and Q are as defined in any one of claims 1 to 25, in which a compound of formula (II):

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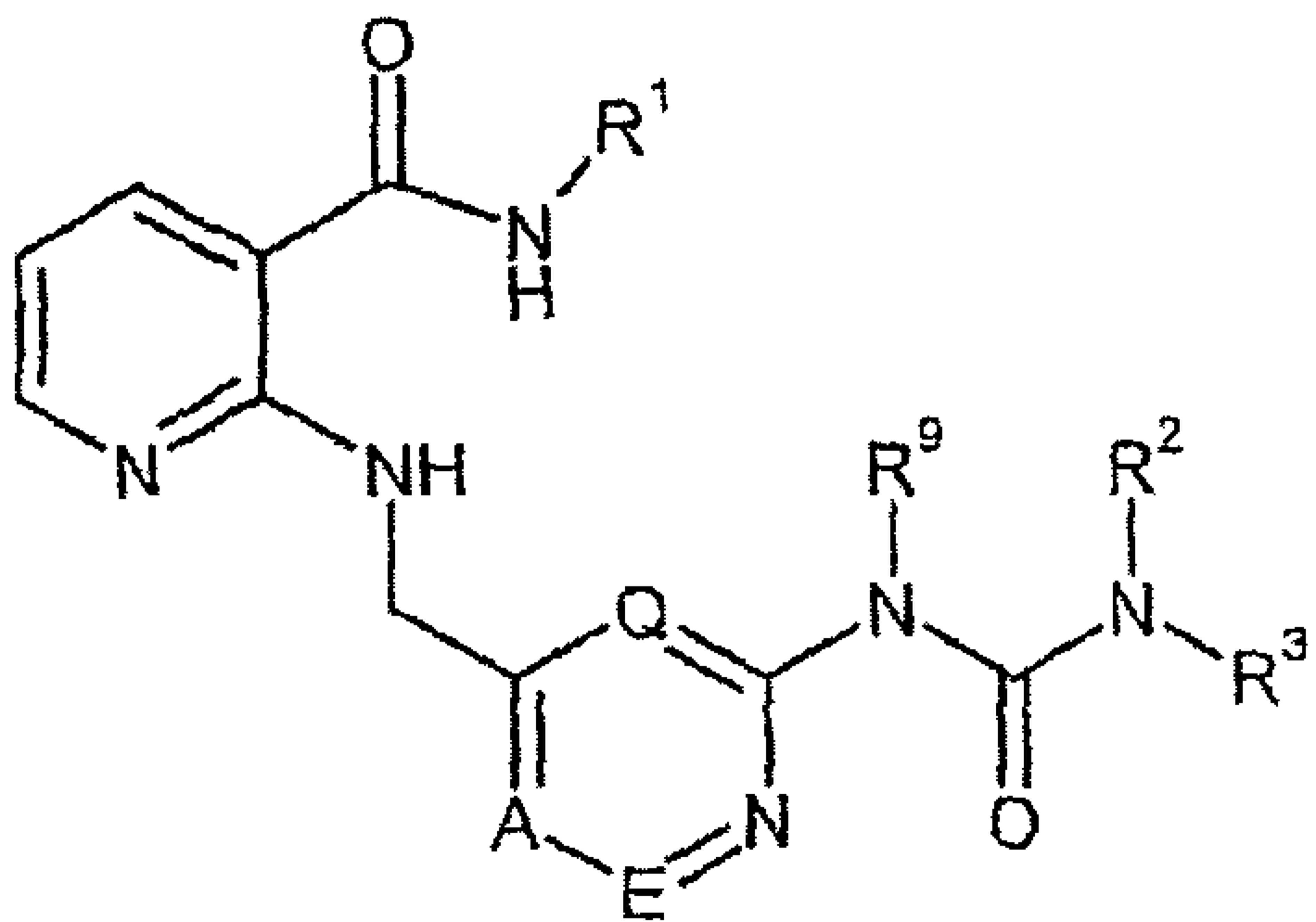


(II),

wherein A, E, Q and R¹ are as defined in any one of claims 1 to 25 and M stands for halogen, is:

- (i) first converted to an amine and subsequently converted to a compound of formula (I) by reaction with a carbamoyl chloride of formula ClCONR²R³, wherein R² and R³ are as defined in any one of claims 1 to 25; or alternatively,
- (ii) reacted with a compound of formula R⁹HNCONR²R³, wherein R², R³ and R⁹ are as defined in any one of claims 1 to 25; or alternatively,
- (iii) first converted to an amine, then converted to a compound of formula (I) by first reacting with a compound of formula ClCO₂Ph and then reacting with a compound of formula HNR²R³, wherein R² and R³ are as defined in any one of claims 1 to 25.

42. A process as claimed in claim 41, wherein in which the compound of formula (II) is reacted with a compound of formula R⁹HNCONR²R³, wherein R², R³ and R⁹ are as defined in any one of claims 1 to 25.



(I)