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ABSTRACT

Title: QUINAZOLINE DERIVATIVES

Novel quinazolineamide derivatives of the formula (I), in which R^1 - R^4 and X have the meanings indicated in claim 1, are HSP90 inhibitors and can be used for preparation of a medicament for the treatment of diseases in which the inhibition, regulation and/or modulation of HSP90 plays a role.

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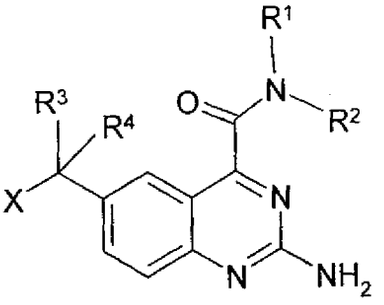
We claim:

~~Patent Claims~~

1. Compounds of the formula I



I

in which

R^1, R^2 each, independently of one another, denote H, A, $(CH_2)_nHet$ or $(CH_2)_nAr$,

R^1 and R^2, together with the N atom to which they are bonded, also denote a saturated, unsaturated or aromatic mono- or bicyclic heterocycle, which may contain a further 1 to 3 N, O and/or S atoms and which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nHet$, $(CH_2)_nAr$, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nNH_2$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, NHCOA, NA'COA, $CONH_2$, CONHA, CONAA', $OC(=O)(CH_2)_pNH_2$ and/or =O (carbonyl oxygen),

R^3, R^4 each, independently of one another, denote H, Hal, A, $(CH_2)_nHet$, $(CH_2)_nAr$, $(CH_2)_nCOHet$ or $(CH_2)_nC(=CH_2)CONR^5R^6$,

R^3 and R^4, together with the C atom to which they are bonded, also denote a saturated or unsaturated monocyclic C3-C10-carbocycle, which may contain a further 1 to 3 N, O and/or S atoms and which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nNH_2$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, NHCOA, NA'COA, $CONH_2$, CONHA, CONAA', $OC(=O)(CH_2)_pNH_2$ and/or =O (carbonyl oxygen),

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	X	denotes NR^5R^6, $CONR^5R^6$, $CH_2NR^5R^6$, $COOR^5$, $-OR^5$, CH_2OR^5, COHet, Het, $CONH(CH_2)_pCN$ or $CONH(CH_2)_pNR^5R^6$,
	R^5, R^6	each, independently of one another, denote H, A, $(CH_2)_nHet$ or $(CH_2)_nAr$,
	Ar	denotes phenyl, naphthyl, tetrahydronaphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, Hal, $(CH_2)_nOA$, $(CH_2)_nOH$, $(CH_2)_nCN$, SA, SOA, SO_2A, NO_2, C≡CH, $(CH_2)_nCOOH$, CHO, $(CH_2)_nCOOA$, $CONH_2$, CONHA, CONAA', NHCOA, CH(OH)A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNAA'$, $(CH_2)_nNHSO_2A$, $SO_2NH(CH_2)_nNH_2$, SO_2NH_2, SO_2NHA, SO_2NAA', $CONH(CH_2)_nCOOA$, $CONH(CH_2)_nCOOH$, $NHCO(CH_2)_nCOOA$, $NHCO(CH_2)_nCOOH$, $CONH(CH_2)_nNH_2$, $CONH(CH_2)_nNHA$, $CONH(CH_2)_nNAA'$, $CONH(CH_2)_nCN$ and/or $(CH_2)_nCH(NH_2)COOH$,
	Het	denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, OA, OH, phenyl, SH, $S(O)_mA$, Hal, NO_2, CN, COA, COOA, COObenzyl, $CONH_2$, CONHA, CONAA', SO_2NH_2, NH_2, NHA, NAA', NHCOA, $NHSO_2A$ and/or =O (carbonyl oxygen),
	A, A'	each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which 1-3 non-adjacent CH_2 groups may be replaced by O, S, SO, SO_2, NH, NMe or NEt, and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl, or cyclic alkyl having 3-8 C atoms,
	Hal	denotes F, Cl, Br or I,
	n	denotes 0, 1, 2, 3 or 4,
	p	denotes 1, 2, 3 or 4,

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and pharmaceutically usable salts and stereoisomers thereof, including mixtures thereof in all ratios.

2. Compounds according to Claim 1 in which

R^1 and R^2, together with the N atom to which they are bonded, denotes an unsubstituted saturated, unsaturated or aromatic mono- or bicyclic heterocycle, which may contain a further 1 to 2 N, O and/or S atoms,

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

3. Compounds according to Claim 1 or 2 in which

R^3, R^4 each, independently of one another, denotes H, A, $(CH_2)_nCOHet$ or $(CH_2)_nC(=CH_2)CONR^5R^6$,

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

4. Compounds according to one or more of Claims 1-3 in which

R^3 and R^4, together with the C atom to which they are bonded, also denote an unsubstituted saturated monocyclic C3-C6-carbocycle, which may contain a further 1 to 3 N, O and/or S atoms,

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

5. Compounds according to one or more of Claims 1-4 in which

X denotes $CONR^5R^6$, $COOR^5$, COHet, Het, $CONH(CH_2)_pCN$ or $CONH(CH_2)_pNR^5R^6$,

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

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6. Compounds according to one or more of Claims 1-5 in which
R^5, R^6 each, independently of one another, denote H, A or $(CH_2)_nHet$,
and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

7. Compounds according to one or more of Claims 1-6 in which
Het denote pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, piperazinyl, pyrazinyl, pyridazinyl, morpholinyl, azepanyl, azetidinyl, pyrrolidinyl or piperidinyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, OA, OH, Hal, CN and/or =O (carbonyl oxygen),
and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

8. Compounds according to one or more of Claims 1-7 in which
A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which 1-2 non-adjacent CH_2 groups may be replaced by O, NH, NMe or NEt, and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl,
or cyclic alkyl having 3-8 C atoms,
and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

9. Compounds according to one or more of Claims 1-8 in which
R^1 and R^2, together with the N atom to which they are bonded, denote an unsubstituted saturated, unsaturated or aromatic mono- or bicyclic heterocycle, which may contain a further 1 to 2 N, O and/or S atoms,
R^3, R^4 each, independently of one another, denote H, A, $(CH_2)_nCOHet$ or $(CH_2)_nC(=CH_2)CONR^5R^6$,

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R^3 and R^4, together with the C atom to which they are bonded, also denote an unsubstituted saturated monocyclic C3-C6-carbocycle, which may contain a further 1 to 3 N, O and/or S atoms,

X denotes $CONR^5R^6$, $COOR^5$, $COHet^1$, Het^1, $CONH(CH_2)_pCN$ or $CONH(CH_2)_pNR^5R^6$,

Het denotes pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, piperazinyl, pyrazinyl, pyridazinyl, morpholinyl, azepanyl, azetidinyl, pyrrolidinyl or piperidinyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, OA, OH, Hal, CN and/or =O (carbonyl oxygen),

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which 1-2 non-adjacent CH_2 groups may be replaced by O, NH, NMe or NEt, and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl,
or cyclic alkyl having 3-8 C atoms,

Hal denotes F, Cl, Br or I,

n denotes 0, 1, 2, 3 or 4,

p denotes 1, 2, 3 or 4,

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

10. Compounds according to Claim 1 selected from the group

Compound No.	Name and/or structure
"A1"	Ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-acetate
"A2"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetic

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	acid
"A3"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-acetamide
"A4"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5,5-difluoropentanamide
"A5"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-cyclobutanecarboxamide
"A6"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethylacetamide
"A7"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-tert-butylacetamide
"A8"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N,N-diethylacetamide
"A9"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N,N-dimethylacetamide
"A10"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-N-methylacetamide
"A11"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N-(2-hydroxyethyl)-N-methylacetamide
"A12"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-hydroxyethyl)-N-ethyiacetamide
"A13"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-pyrrolidin-1-ylethanone
"A14"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-(2-methylpyrrolidin-1-yl)ethanone
"A15"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-(2,5-dimethylpyrrolidin-1-yl)ethanone
"A16"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-methylacetamide
"A17"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-(4-methylpiperazin-1-yl)ethanone

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"A18"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-piperazin-1-ylethanone
"A19"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-methyl-N-[(3-methylimidazol-4-yl)methyl]acetamide
"A20"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-tert-butylcyclopropanecarboxamide
"A21"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethylcyclopropanecarboxamide
"A22"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N,N-dimethylcyclopropanecarboxamide
"A23"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-N-methylcyclopropanecarboxamide
"A24"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N,N-diethylcyclopropanecarboxamide
"A25"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-hydroxyethyl)-N-methylcyclopropanecarboxamide
"A26"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-hydroxyethyl)-N-ethylcyclopropanecarboxamide
"A27"	[2-Amino-6-[1-(pyrrolidine-1-carbonyl)cyclopropyl]-quinazolin-4-yl]isoindolin-2-ylmethanone
"A28"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-dimethylaminoethyl)-N-ethylcyclopropanecarboxamide
"A29"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-tert-butylcyclobutanecarboxamide
"A30"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethylcyclobutanecarboxamide
"A31"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-methylcyclobutanecarboxamide
"A32"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-propylcyclobutanecarboxamide
"A33"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-

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	amino-2-oxoethyl)cyclobutanecarboxamide
"A34"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-isobutylcyclobutanecarboxamide
"A35"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-tert-butyl-2-methylpropanamide
"A36"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-2-methylpropanamide
"A37"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-isobutyl-2-methylpropanamide
"A38"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-propyl-2-methylpropanamide
"A39"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-amino-2-oxoethyl)-2-methylpropanamide
"A40"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N-(2-cyanoethyl)-2-methylpropanamide
"A41"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-methyl-5,5-difluoropentanamide
"A42"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-5,5-difluoropentanamide
"A43"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethylpentanamide
"A44"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethylhexanamide
"A45"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-5-methylhexanamide
"A46"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-4-methylpentanamide
"A47"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-3-methylpentanamide
"A48"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-3-methylbutanamide

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"A49"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-4-(4-methylpiperazin-1-yl)-4-oxobutanamide
"A50"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N'-ethyl-2-methylenepentanediamide
"A51"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-N-ethyl-5,5-difluoropentanamide
"A52"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-5,5-difluoro-N-(1,1,3,3-tetramethylbutyl)pentanamide
"A53"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethylcyclopentanecarboxamide
"A54"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyltetrahydropyran-4-carboxamide
"A55"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-2-methylpentanamide
"A56"	Ethyl 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-cyclopropanecarboxylate
"A57"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-cyclopropanecarboxylic acid
"A59"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N-(2-dimethylaminoethyl)-N-ethylacetamide
"A61"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-cyclobutanecarboxylic acid
"A62"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylpropanoic acid
"A63"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5,5-difluoropentanoic acid
"A64"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-pentanoic acid
"A65"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-hexanoic acid

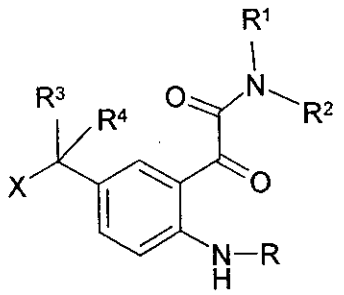
"A66"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-5,5-difluoropentanoic acid
"A67"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl-2-methylpentanoic acid
"A68"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-cyclopentanecarboxylic acid
"A69"	2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-tetrahydropyran-4-carboxylic acid
"A70"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5-methylhexanoic acid
"A71"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]4-methylpentanoic acid
"A72"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-3-methylpentanoic acid
"A73"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-3-methylbutanoic acid
"A74"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-carbamoylpent-4-enoic acid
"A75"	1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-(4-methylpiperazin-1-yl)-4-oxobutanoic acid
"A76"	[2-Amino-6-[(4-methylpiperazin-1-yl)methyl]quinazolin-4-yl]-isoindolin-2-ylmethanone
"A77"	N-Dimethyl-2-amino-6-(1-ethylcarbamoylcyclobutyl)-quinazoline-4-carboxamide
"A78"	N-Methylpropyl-2-amino-6-(1-ethylcarbamoylcyclobutyl)-quinazoline-4-carboxamide
"A79"	N-Diethyl-2-amino-6-(1-ethylcarbamoylcyclobutyl)-quinazoline-4-carboxamide
"A80"	N-Benzylmethyl-2-amino-6-(1-ethylcarbamoylcyclobutyl)-quinazoline-4-carboxamide

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

11. Process for the preparation of compounds of the formula I according to Claims 1-10 and pharmaceutically usable salts, tautomers and stereoisomers thereof, characterised in that

a) for the preparation of compounds of the formula I in which X denotes COOA,

a compound of the formula II



II

in which

R^1, R^2, R^3 and R^4 have the meanings indicated in Claim 1,

R denotes an amino-protecting group,

X denotes COOA,

and

A has the meaning indicated in Claim 1,

is reacted with a compound of the formula III

$$Y_3Si\text{-}N{=}C{=}N\text{-}SiY_3 \qquad \text{III}$$

in which

Y denotes alkyl having 1-4 C atoms,

or

b) a radical X is converted into another radical X by
   i) hydrolysing an ester or
   ii) converting an acid into an amide using an amine,

and/or a base or acid of the formula I is converted into one of its salts.

12. Medicaments comprising at least one compound according to Claim 1-10 and/or pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

13. Compounds according to Claim 1-10, and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, for use for the preparation of a medicament for the treatment or prevention of tumour diseases, viral diseases, for immune suppression in transplants, inflammation-induced diseases, cystic fibrosis, diseases associated with angiogenesis, infectious diseases, autoimmune diseases, ischaemia, fibrogenetic diseases,
for the promotion of nerve regeneration,
for inhibiting the growth of cancer, tumour cells and tumour metastases,
for the protection of normal cells against toxicity caused by chemotherapy,
for the treatment of diseases in which incorrect protein folding or aggregation is a principal causal factor.

14. Medicaments comprising at least one compound according to Claim 1-10 and/or pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

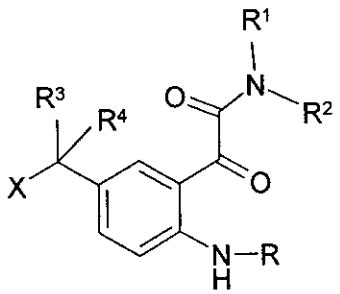
15. Set (kit) consisting of separate packs of

(a) an effective amount of a compound according to Claim 1-10 and/or pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios,

and

(b) an effective amount of a further medicament active ingredient.

16. Compounds of the formula II



II

in which

R^1, R^2 each, independently of one another, denote H, A, $(CH_2)_nHet$ or $(CH_2)_nAr$,

R^1 and R^2, together with the N atom to which they are bonded, also denote a saturated, unsaturated or aromatic mono- or bicyclic heterocycle, which may contain a further 1 to 3 N, O and/or S atoms and which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nHet$, $(CH_2)_nAr$, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nNH_2$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, NHCOA, NA'COA, $CONH_2$, CONHA, CONAA', $OC(=O)(CH_2)_pNH_2$ and/or =O (carbonyl oxygen),

R^3, R^4 each, independently of one another, denote H, Hal, A, $(CH_2)_nHet$, $(CH_2)_nAr$, $(CH_2)_nCOHet$ or $(CH_2)_nC(=CH_2)CONR^5R^6$,

R^3 and R^4, together with the C atom to which they are bonded, also denote a saturated or unsaturated monocyclic C3-C10-carbocycle, which may contain a further 1 to 3 N, O and/or S atoms and which is unsubstituted or mono-, di- or trisubstituted by Hal,

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A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_rNH_2$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, NHCOA, NA'COA, $CONH_2$, CONHA, CONAA', $OC(=O)(CH_2)_pNH_2$ and/or =O (carbonyl oxygen),

R denotes tert-butyloxycarbonyl,

X denotes $COOR^5$,

R^5 denotes A,

Ar denotes phenyl, naphthyl, tetrahydronaphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, Hal, $(CH_2)_nOA$, $(CH_2)_nOH$, $(CH_2)_nCN$, SA, SOA, SO_2A, NO_2, C≡CH, $(CH_2)_nCOOH$, CHO, $(CH_2)_nCOOA$, $CONH_2$, CONHA, CONAA', NHCOA, CH(OH)A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNAA'$, $(CH_2)_nNHSO_2A$, $SO_2NH(CH_2)_nNH_2$, SO_2NH_2, SO_2NHA, SO_2NAA', $CONH(CH_2)_nCOOA$, $CONH(CH_2)_nCOOH$, $NHCO(CH_2)_nCOOA$, $NHCO(CH_2)_nCOOH$, $CONH(CH_2)_nNH_2$, $CONH(CH_2)_nNHA$, $CONH(CH_2)_nNAA'$, $CONH(CH_2)_nCN$ and/or $(CH_2)_nCH(NH_2)COOH$,

Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, OA, OH, phenyl, SH, $S(O)_mA$, Hal, NO_2, CN, COA, COOA, COObenzyl, $CONH_2$, CONHA, CONAA', SO_2NH_2, NH_2, NHA, NAA', NHCOA, $NHSO_2A$ and/or =O (carbonyl oxygen),

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which 1-3 non-adjacent CH_2 groups may be replaced by O, S, SO, SO_2, NH, NMe or NEt, and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl, or cyclic alkyl having 3-8 C atoms,

Hal denotes F, Cl, Br or I,

n denotes 0, 1, 2, 3 or 4,

p denotes 1, 2, 3 or 4,

and salts thereof.

Dated this 22nd day of June 2012

OF L.S. DAVAR & CO.
APPLICANTS AGENT

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Quinazoline derivatives

BACKGROUND OF THE INVENTION

The invention was based on the object of finding novel compounds having valuable properties, in particular those which can be used for the preparation of medicaments.

The present invention relates to compounds in which the inhibition, regulation and/or modulation of HSP90 plays a role, furthermore to pharmaceutical compositions which comprise these compounds, and to the use of the compounds for the treatment of diseases in which HSP90 plays a role.

The correct folding and conformation of proteins in cells is ensured by molecular chaperones and is critical for the regulation of the equilibrium between protein synthesis and degradation. Chaperones are important for the regulation of many central functions of cells, such as, for example, cell proliferation and apoptosis (Jolly and Morimoto, 2000; Smith et al., 1998; Smith, 2001).

Heat shock proteins (HSPs)

The cells of a tissue react to external stress, such as, for example, heat, hypoxia, oxidative stress, or toxic substances, such as heavy metals or alcohols, with activation of a number of chaperones which are known under the term "heat shock proteins" (HSPs).

The activation of HSPs protects the cell against damage initiated by such stress factors, accelerates the restoration of the physiological state and results in a stress-tolerant state of the cell.

Besides this originally discovered protective mechanism promoted by HSPs against external stress, further important chaperone functions have also been described in the course of time for individual HSPs under normal stress-free conditions. Thus, various HSPs regulate, for example,

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correct folding, intracellular localisation and function or regulated degradation of a number of biologically important proteins of cells.

HSPs form a gene family with individual gene products whose cellular expression, function and localisation differs in different cells. The naming and classification within the family is carried out on the basis of their molecular weight, for example HSP27, HSP70, and HSP90.

Some human diseases are based on incorrect protein folding (see review, for example, Tytell et al., 2001; Smith et al., 1998). The development of therapies which engages in the mechanism of the chaperone-dependent protein folding could therefore be useful in such cases. For example, incorrectly folded proteins result in aggregation of protein with neurodegenerative progression in the case of Alzheimer's disease, prion diseases or Huntington's syndrome. Incorrect protein folding may also result in loss of wild-type function, which can have the consequence of incorrectly regulated molecular and physiological function.

HSPs are also ascribed great importance in tumour diseases. There are, for example, indications that the expression of certain HSPs correlates with the stage of progression of tumours (Martin et al., 2000; Conroy et al., 1996; Kawanishi et al., 1999; Jameel et al., 1992; Hoang et al., 2000; Lebeau et al., 1991).

The fact that HSP90 plays a role in a number of central oncogenic signalling pathways in the cell and certain natural products having cancer-inhibiting activity target HSP90 has led to the concept that inhibition of the function of HSP90 would be sensible in the treatment of tumour diseases. An HSP90 inhibitor, 17- allylamino-17-demethoxygeldanamycin (17AAG), a derivative of geldanamycin, is currently undergoing clinical trials.

HSP90

HSP90 represents approximately 1-2% of the total cellular protein mass. It

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is usually in the form of a dimer in the cell and is associated with a multiplicity of proteins, so-called co-chaperones (see, for example, Pratt, 1997). HSP90 is essential for the vitality of cells (Young et al., 2001) and plays a key role in the response to cellular stress by interaction with many proteins whose native folding has been modified by external stress, such as, for example, heat shock, in order to restore the original folding or to prevent aggregation of the proteins (Smith et al.,1998).

There are also indications that HSP90 is of importance as buffer against the effects of mutations, presumably through correction of incorrect protein folding caused by the mutation (Rutherford and Lindquist, 1998).

In addition, HSP90 also has a regulatory importance. Under physiological conditions, HSP90, together with its homologue in the endoplasmatic reticulum, GRP94, plays a role in the cell balance for ensuring the stability of the conformation and maturing of various client key proteins. These can be divided into three groups: receptors for steroid hormones, Ser/Thr or tyrosine kinases (for example ERBB2, RAF-1, CDK4 and LCK) and a collection of various proteins, such as, for example, mutated p53 or the catalytic subunit of telomerase hTERT. Each of these proteins takes on a key role in the regulation of physiological and biochemical processes of cells.

The preserved HSP90 family in humans consists of four genes, cytosolic HSP90α, the inducible HSP90β isoform (Hickey et al., 1989), GRP94 in the endoplasmatic reticulum (Argon et al., 1999) and HSP75/TRAP1 in the mitochondrial matrix (Felts et al., 2000). It is assumed that all members of the family have a similar mode of action, but, depending on their localisation in the cell, bind to different client proteins. For example, ERBB2 is a specific client protein of GRP94 (Argon et al., 1999), while the type 1 receptor of tumour necrosis factor (TNFR1) or the retinoblastoma protein (Rb) have been found to be clients of TRAP1 (Song et al., 1995; Chen et al., 1996).

HSP90 is involved in a number of complex interactions with a large number of client proteins and regulatory proteins (Smith, 2001). Although precise molecular details have not yet been clarified, biochemical experiments and

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investigations with the aid of X-ray crystallography in recent years have increasingly been able to decipher details of the chaperone function of HSP90 (Prodromou et al., 1997; Stebbins et al., 1997). Accordingly, HSP90 is an ATP-dependent molecular chaperone (Prodromou et al, 1997), with dimerisation being important for ATP hydrolysis. The binding of ATP results in the formation of a toroidal dimer structure, in which the two N-terminal domains come into close contact with one another and act as a switch in the conformation. (Prodromou and Pearl, 2000).

Known HSP90 inhibitors

The first class of HSP90 inhibitors to be discovered were benzoquinone ansamycins with the compounds herbimycin A and geldanamycin. Originally, the reversion of the malignant phenotype in fibroblasts which had been induced by transformation with the v-Src oncogene was detected with them (Uehara et al., 1985).

Later, a strong antitumoural activity was demonstrated in vitro (Schulte et al., 1998) and in vivo in animal models (Supko et al., 1995).

Immune precipitation and investigations on affinity matrices then showed that the principal mechanism of action of geldanamycin involves binding to HSP90 (Whitesell et al., 1994; Schulte and Neckers, 1998). In addition, X-ray crystallographic studies have shown that geldanamycin competes for the ATP binding site and inhibits the intrinsic ATPase activity of HSP90 (Prodromou et al., 1997; Panaretou et al., 1998). This prevents the formation of the multimeric HSP90 complex, with its property of functioning as chaperone for client proteins. As a consequence, client proteins are degraded via the ubiquitin-proteasome pathway.

The geldanamycin derivative 17- allylamino-17-demethoxygeldanamycin (17AAG) showed an unchanged property in the inhibition of HSP90, the degradation of client proteins and antitumoural activity in cell cultures and in xenograft tumour models (Schulte et al, 1998; Kelland et al, 1999), but had

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significantly lower liver cytotoxicity than geldanamycin (Page et al. 1997). 17AAG is currently undergoing phase I/II clinical trials.

Radicicol, a macrocyclic antibiotic, likewise exhibited revision of the v-Src and v-Ha-Ras-induced malignant phenotype of fibroblasts (Kwon et all 1992; Zhao et al, 1995). Radicicol degrades a large number of signal proteins as a consequence of HSP90 inhibition (Schulte et al., 1998). X-ray crystallographic studies have shown that radicicol likewise binds to the N-terminal domain of HSP90 and inhibits the intrinsic ATPase activity (Roe et al., 1998).

As is known, antibiotics of the coumarine type bind to the ATP binding site of the HSP90 homologue DNA gyrase in bacteria. The coumarine, novobiocin, binds to the carboxy-terminal end of HSP90, i.e. to a different site in HSP90 than the benzoquinone-ansamycins and radicicol, which bind to the N-terminal end of HSP90. (Marcu et al., 2000b).

The inhibition of HSP90 by novobiocin results in degradation of a large number of HSP90-dependent signal proteins (Marcu et al., 2000a).

The degradation of signal proteins, for example ERBB2, was demonstrated using PU3, an HSP90 inhibitor derived from purines. PU3 causes cell cycle arrest and differentiation in breast cancer cell lines (Chiosis et al., 2001).

HSP90 as therapeutic target

Due to the participation of HSP90 in the regulation of a large number of signalling pathways which are of crucial importance in the phenotype of a tumour, and the discovery that certain natural products exert their biological effect through inhibition of the activity of HSP90, HSP90 is currently being tested as a novel target for the development of a tumour therapeutic agent (Neckers et al., 1999).

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The principal mechanism of action of geldanamycin, 17AAG, and radicicol includes the inhibition of the binding of ATP to the ATP binding site at the N-terminal end of the protein and the resultant inhibition of the intrinsic ATPase activity of HSP90 (see, for example, Prodromou et al., 1997; Stebbins et al., 1997; Panaretou et al., 1998). Inhibition of the ATPase activity of HSP90 prevents the recruitment of co-chaperones and favours the formation of an HSP90 heterocomplex, which causes client proteins to undergo degradation via the ubiquitin-proteasome pathway (see, for example, Neckers et al., 1999; Kelland et al., 1999). The treatment of tumour cells with HSP90 inhibitors results in selective degradation of important proteins having fundamental importance for processes such as cell proliferation, regulation of the cell cycle and apoptosis. These processes are frequently deregulated in tumours (see, for example, Hostein et al., 2001).

An attractive rationale for the development of an inhibitor of HSP90 is that a strong tumour-therapeutic action can be achieved by simultaneous degradation of a plurality of proteins which are associated with the transformed phenotype.

In detail, the present invention relates to compounds which inhibit, regulate and/or modulate HSP90, to compositions which comprise these compounds, and to methods for the use thereof for the treatment of HSP90-induced diseases, such as tumour diseases, viral diseases, such as, for example, hepatitis B (Waxman, 2002); immune suppression in transplants (Bijlmakers, 2000 and Yorgin, 2000); inflammation-induced diseases (Bucci, 2000), such as rheumatoid arthritis, asthma, multiple sclerosis, type 1 diabetes, lupus erythematosus, psoriasis and inflammatory bowel disease; cystic fibrosis (Fuller, 2000); diseases associated with angiogenesis (Hur, 2002 and Kurebayashi, 2001), such as, for example, diabetic retinopathy, haemangiomas, endometriosis and tumour angiogenesis; infectious diseases; autoimmune diseases; ischaemia; promotion of nerve regeneration (Rosen et al., WO 02/09696; Degranco et al., WO 99/51223; Gold, US 6,210,974 B1); fibrogenetic diseases, such as, for example,

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scleroderma, polymyositis, systemic lupus, cirrhosis of the liver, keloid formation, interstitial nephritis and pulmonary fibrosis (Strehlow, WO 02/02123).

The invention also relates to the use of the compounds according to the invention for the protection of normal cells against toxicity caused by chemotherapy, and to the use in diseases where incorrect protein folding or aggregation is a principal causal factor, such as, for example, scrapie, Creutzfeldt-Jakob disease, Huntington's or Alzheimer's (Sittler, Hum. Mol. Genet., 10, 1307, 2001; Tratzelt et al., Proc. Nat. Acad. Sci., 92, 2944, 1995; Winklhofer et al., J. Biol. Chem., 276, 45160, 2001).

WO 01/72779 describes purine compounds and the use thereof for the treatment of GRP94 (homologue or paralogue of HSP90)-induced diseases, such as tumour diseases, where the cancerous tissue includes a sarcoma or carcinoma selected from the group consisting of fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumour, leiosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, syringocarcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinomas, bone marrow carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonic carcinoma, Wilm's tumour, cervical cancer, testicular tumour, lung carcinoma, small-cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, haemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukaemia, lymphoma, multiple myeloma, Waldenström's macroglobulinaemia and heavy chain disease.

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WO 01/72779 furthermore discloses the use of the compounds mentioned therein for the treatment of viral diseases, where the viral pathogen is selected from the group consisting of hepatitis type A, hepatitis type B, hepatitis type C, influenza, varicella, adenovirus, herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), cattle plague, rhinovirus, echovirus, rotavirus, respiratory syncytial virus (RSV), papillomavirus, papovavirus, cytomegalovirus, echinovirus, arbovirus, huntavirus, Coxsackie virus, mumps virus, measles virus, rubella virus, polio virus, human immunodeficiency virus type I (HIV-I) and human immunodeficiency virus type II (HIV-II).

WO 01/72779 furthermore describes the use of the compounds mentioned therein for GRP94 modulation, where the modulated biological GRP94 activity causes an immune reaction in an individual, protein transport from the endoplasmatic reticulum, recovery from hypoxic/anoxic stress, recovery from malnutrition, recovery from heat stress, or combinations thereof, and/or where the disorder is a type of cancer, an infectious disease, a disorder associated with disrupted protein transport from the endoplasmatic reticulum, a disorder associated with ischaemia/reperfusion, or combinations thereof, where the the disorder associated with ischaemia/reperfusion is a consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress.

Finally, WO 01/72779 describes the use of an effective amount of a GRP94 protein modulator for the preparation of a medicament for changing a subsequent cellular reaction to an ischaemic state in a tissue site in an individual, by treatment of the cells at the tissue site with the GRP94 protein

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modulator in order that the GRP94 activity in cells is increased to such an extent that a subsequent cellular reaction to an ischaemic state is changed, where the subsequent ischaemic condition is preferably the consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress, or where the tissue site is the donor tissue for a transplant.

A. Kamal et al. in Trends in Molecular Medicine, Vol. 10 No. 6 June 2004, describe therapeutic and diagnostic applications of HSP90 activation, inter alia for the treatment of diseases of the central nervous system and of cardiovascular diseases.

The identification of small compounds which specifically inhibit, regulate and/or modulate HSP90 is therefore desirable and an aim of the present invention.

It has been found that the compounds according to the invention and salts thereof have very valuable pharmacological properties while being well tolerated.
In particular, they exhibit HSP90-inhibiting properties.

The present invention therefore relates to compounds according to the invention as medicaments and/or medicament active ingredients in the treatment and/or prophylaxis of the said diseases and to the use of compounds according to the invention for the preparation of a pharmaceutical for the treatment and/or prophylaxis of the said diseases and also to a process for the treatment of the said diseases which comprises the admini-

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stration of one or more compounds according to the invention to a patient in need of such an administration.

The host or patient may belong to any mammallian species, for example a primate species, particularly humans; rodents, including mice, rats and hamsters; rabbits; horses, cows, dogs, cats, etc. Animal models are of interest for experimental investigations, where they provide a model for the treatment of a human disease.

PRIOR ART

WO 00/53169 describes HSP90 inhibition using coumarine or a coumarine derivative.
WO 03/041643 A2 discloses HSP90-inhibiting zearalanol derivatives.
HSP90-inhibiting indazole derivatives are known from WO 06/010595 and WO 02/083648.

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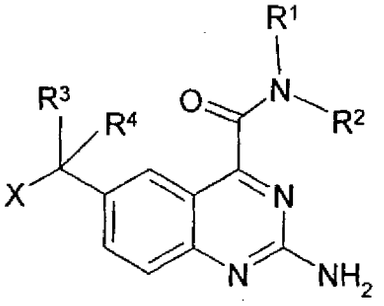
SUMMARY OF THE INVENTION

The invention relates to compounds of the formula I



I

in which

R^1, R^2 each, independently of one another, denote H, A, $(CH_2)_nHet$ or $(CH_2)_nAr$,

R^1 and R^2, together with the N atom to which they are bonded, also denote a saturated, unsaturated or aromatic mono- or bicyclic heterocycle, which may contain a further 1 to 3 N, O and/or S atoms and which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nHet$, $(CH_2)_nAr$, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nNH_2$,

		$(CH_2)_nCOOH$, $(CH_2)_nCOOA$, NHCOA, NA'COA, $CONH_2$, CONHA, CONAA', $OC(=O)(CH_2)_pNH_2$ and/or =O (carbonyl oxygen),
	R^3, R^4	each, independently of one another, denote H, Hal, A, $(CH_2)_nHet$, $(CH_2)_nAr$, $(CH_2)_nCOHet$ or $(CH_2)_nC(=CH_2)CONR^5R^6$,
	R^3 and R^4,	together with the C atom to which they are bonded, also denote a saturated or unsaturated monocyclic C3-C10-carbocycle, which may contain a further 1 to 3 N, O and/or S atoms and which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nNH_2$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, NHCOA, NA'COA, $CONH_2$, CONHA, CONAA', $OC(=O)(CH_2)_pNH_2$ and/or =O (carbonyl oxygen),
	X	denotes NR^5R^6, $CONR^5R^6$, $CH_2NR^5R^6$, $COOR^5$, $-OR^5$, CH_2OR^5, COHet, Het, $CONH(CH_2)_pCN$ or $CONH(CH_2)_pNR^5R^6$,
	R^5, R^6	each, independently of one another, denote H, A, $(CH_2)_nHet$ or $(CH_2)_nAr$,
	Ar	denotes phenyl, naphthyl, tetrahydronaphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, Hal, $(CH_2)_nOA$, $(CH_2)_nOH$, $(CH_2)_nCN$, SA, SOA, SO_2A, NO_2, C≡CH, $(CH_2)_nCOOH$, CHO, $(CH_2)_nCOOA$, $CONH_2$, CONHA, CONAA', NHCOA, CH(OH)A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNAA'$, $(CH_2)_nNHSO_2A$, $SO_2NH(CH_2)_nNH_2$, SO_2NH_2, SO_2NHA, SO_2NAA', $CONH(CH_2)_nCOOA$, $CONH(CH_2)_nCOOH$, $NHCO(CH_2)_nCOOA$, $NHCO(CH_2)_nCOOH$, $CONH(CH_2)_nNH_2$, $CONH(CH_2)_nNHA$, $CONH(CH_2)_nNAA'$, $CONH(CH_2)_nCN$ and/or $(CH_2)_nCH(NH_2)COOH$,
	Het	denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, OA, OH, phenyl, SH, $S(O)_mA$, Hal, NO_2, CN, COA, COOA, COObenzyl, $CONH_2$, CONHA, CONAA', SO_2NH_2, NH_2, NHA, NAA', NHCOA, $NHSO_2A$ and/or =O (carbonyl oxygen),

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which 1-3 non-adjacent CH_2 groups may be replaced by O, S, SO, SO_2, NH, NMe or Net, and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl, or cyclic alkyl having 3-8 C atoms,

Hal denotes F, Cl, Br or I,

n denotes 0, 1, 2, 3 or 4,

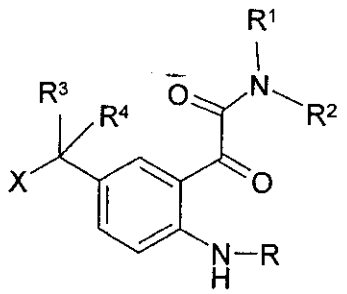
p denotes 1, 2, 3 or 4,

and pharmaceutically usable salts and stereoisomers thereof, including mixtures thereof in all ratios.

The invention relates to the compounds of the formula I and salts thereof and to a process for the preparation of compounds of the formula I and pharmaceutically usable salts, tautomers and stereoisomers thereof, characterised in that

a) for the preparation of compounds of the formula I in which X denotes COOA,

a compound of the formula II



II

in which

R^1, R^2, R^3 and R^4 have the meanings indicated in Claim 1,

R denotes an amino-protecting group,

X denotes COOA,

and

A has the meaning indicated in Claim 1,

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is reacted with a compound of the formula III

$$Y_3Si\text{-}N{=}C{=}N\text{-}SiY_3 \qquad \text{III}$$

in which

Y denotes alkyl having 1-4 C atoms,

or

b) a radical X is converted into another radical X by

i) hydrolysing an ester or

ii) converting an acid into an amide using an amine,

and/or a base or acid of the formula I is converted into one of its salts.

Compounds of the formula I are also taken to mean the hydrates and solvates of these compounds, furthermore pharmaceutically usable derivatives.
The invention also relates to the stereoisomers (E, Z isomers) and the hydrates and solvates of these compounds. Solvates of the compounds are taken to mean adductions of inert solvent molecules onto the compounds which form owing to their mutual attractive force. Solvates are, for example, mono- or dihydrates or alcoholates.

Pharmaceutically usable derivatives are taken to mean, for example, the salts of the compounds according to the invention and also so-called pro-drug compounds.
Prodrug derivatives are taken to mean compounds of the formula I which have been modified with, for example, alkyl or acyl groups, sugars or oligo-peptides and which are rapidly cleaved in the organism to give the effective compounds according to the invention.

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These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115, 61-67 (1995).

The expression "effective amount" means the amount of a medicament or pharmaceutical active ingredient that causes a biological or medical response which is sought or desired, for example, by a researcher or physician in a tissue, system, animal or human.

In addition, the expression "therapeutically effective amount" means an amount which, compared with a corresponding subject who has not received this amount, has the following consequence:

improved healing treatment, healing, prevention or elimination of a disease, syndrome, condition, complaint, disorder or side effects or also the reduction in the advance of a disease, complaint or disorder.

The term "therapeutically effective amount" also encompasses the amounts which are effective for increasing normal physiological function.

The invention also relates to mixtures of the compounds of the formula I according to the invention, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.

These are particularly preferably mixtures of stereoisomeric compounds.

For all radicals which occur more than once, their meanings are independent of one another.

Above and below, the radicals and parameters R^1, R^2, R^3, R^4 and X have the meanings indicated for the formula I, unless expressly indicated otherwise.

Carbamoyl denotes aminocarbonyl.

BOC or Boc denotes tert-butyloxycarbonyl.

A or A' preferably denotes alkyl, is unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms. A or A' particularly preferably denotes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-

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butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1- , 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1- , 2- , 3- or 4-methylpentyl, 1,1- , 1,2- , 1,3- , 2,2- , 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl.

A or A' very particularly preferably denotes alkyl having 1, 2, 3, 4, 5 or 6 C atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl.

A, A' also each denote, independently of one another, unbranched or branched alkyl having 1-10 C atoms, in which 1-3 non-adjacent CH_2 groups may be replaced by O, S, SO, SO_2, NH, NMe, or NEt, such as, for example, 2-methoxyethyl or 3-methylaminopropyl.

A or A' also denotes cyclic alkyl (cycloalkyl). Cycloalkyl preferably denotes cyclopropyl, cyclobutyl, cylopentyl, cyclohexyl or cycloheptyl. Cyclic alkyl furthermore preferably denotes cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl.

Cycloalkylalkylene denotes, for example, cyclopropylmethylene or cyclohexylmethylene.

A,A' particularly preferably denote, in each case independently of one another, unbranched or branched alkyl having 1-10 C atoms, in which 1-2 non-adjacent CH_2 groups may be replaced by O, NH, NMe or NEt and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl,
or cyclic alkyl having 3-8 C atoms.

R^1 and R^2, together with the N atom to which they are bonded, preferably denote an unsubstituted saturated, unsaturated or aromatic mono- or bicyclic heterocycle, which may contain a further 1 to 2 N, O and/or S atoms, where the heterocycle is preferably selected from the group pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, oxazolidine, dihydroindole, isoindoline, tetrahydroquinoline, tetrahydroisoquinoline, tetrahydroquinoxaline.

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Very particular preference is given to isoindoline (2,3-dihydroisoindole).

R^3, R^4, in each case independently of one another, preferably denote, H, A, $(CH_2)_nCOHet$ or $(CH_2)_nC(=CH_2)CONR^5R^6$.

R^3, R^4, in each case independently of one another, very particularly preferably denote H, unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl, or 4-methylpiperazin-1-ylcarbonyl-methyl, H_2N-CO-$C(=CH_2)CH_2$.

R^3, R^4, together with the C atom to which they are bonded, furthermore preferably also denote an unsubstituted saturated monocyclic C3-C6-carbocycle, which may contain a further 1 to 3 N, O and/or S atoms.

R^3, R^4, together with the C atom to which they are bonded, furthermore particularly preferably also denote an unsubstituted saturated monocyclic C3-, C4-, C5- or C6-carbocycle, which may contain a further 1 to 2 N, O and/or S atoms.

X preferably denotes $CONR^5R^6$, $COOR^5$, COHet, Het, $CONH(CH_2)_pCN$ or $CONH(CH_2)_pNR^5R^6$.

X very particularly preferably denotes ethoxycarbonyl, carboxyl, carbamoyl, N-ethylcarbamoyl, N-tert-butylcarbamoyl, N,N-diethylcarbamoyl, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-(2-hydroxyethyl)-N-methylcarbamoyl, N-(2-hydroxyethyl)-N-ethylcarbamoyl, pyrrolidin-1-ylcarbonyl, 2-methylpyrrolidin-1-ylcarbonyl, 2,5-dimethylpyrrolidin-1-ylcarbonyl, N-methylcarbamoyl, 4-methylpiperazin-1-ylcarbonyl, piperazin-1-ylcarbonyl, N-(3-methyl-3H-imidazol-4-ylmethyl)-N-methylcarbamoyl, N-(2-dimethylaminoethyl)-N-ethylcarbamoyl, N-propylcarbamoyl, N-butyl, carbamoyl, N-isobutylcarbamoyl, N-(carbamoylmethyl)carbamoyl, N-(2-cyano-ethyl)carbamoyl, N-(1,1,3,3-tetramethylbutyl)carbamoyl, 4-methylpiperazin-1-yl.

R^5, R^6, in each case independently of one another, preferably denote H, A or $(CH_2)_nHet$.

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Ar denotes, for example, phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, o-, m- or p-(methylsulfonyl)phenyl, o-, m- or p-cyanophenyl, o-, m- or p-acetylphenyl, o-, m- or p-aminosulfonylphenyl, o-, m- or p-carboxyphenyl, o-, m- or p-carboxymethylphenyl, o-, m- or p-carboxymethoxyphenyl, further preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro- or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-dimethyl-4-chlorophenyl.

Ar particularly preferably denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, Hal and/or OA.

Irrespective of further substitutions, Het denotes, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-

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pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benziso-thiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, further preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

The heterocyclic radicals may also be partially or fully hydrogenated.

Het can thus also denote, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-,-2-,-3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8- 3,4-dihydro-2H-benzo-1,4-oxazinyl, further preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxy-phenyl, 3,4-ethylenedioxyphenyl, isoindolinyl, 3,4-(difluoromethylenedioxy)-phenyl, 2,3-dihydrobenzofuran-5- or 6-yl, 2,3-(2-oxomethylenedioxy)phenyl

or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

Het preferably denotes pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, piperazinyl, pyrazinyl, pyridazinyl, morpholinyl, azepanyl, azetidinyl, pyrrolidinyl or piperidinyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, OA, OH, Hal, CN and/or =O (carbonyl oxygen).

n preferably denotes 0, 1 or 2.
p preferably denotes 1 or 2.

The compounds of the formula I may have one or more chiral centres and can therefore occur in various stereoisomeric forms. The formula I encompasses all these forms.
Accordingly, the invention relates, in particular, to the compounds of the formula I in which at least one of the said radicals has one of the preferred meanings indicated above. Some preferred groups of compounds may be expressed by the following sub-formulae Ia to Ih, which conform to the formula I and in which the radicals not designated in greater detail have the meaning indicated for the formula I, but in which

in Ia R^1 and R^2, together with the N atom to which they are bonded, denote an unsubstituted saturated, unsaturated or aromatic mono- or bicyclic heterocycle, which may contain a further 1 to 2 N, O and/or S atoms;

in Ib R^3, R^4 each, independently of one another, denote H, A, $(CH_2)_nCOHet$ or $(CH_2)_nC(=CH_2)CONR^5R^6$;

in Ic R^3 and R^4, together with the C atom to which they are bonded, also denote an unsubstituted saturated monocyclic C3-C6-

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carbocycle, which may contain a further 1 to 3 N, O and/or S atoms;

in Id X denotes $CONR^5R^6$, $COOR^5$, COHet, Het, $CONH(CH_2)_pCN$ or $CONH(CH_2)_pNR^5R^6$;

in Ie R^5, R^6 each, independently of one another, denote H, A or $(CH_2)_nHet$;

in If Het denotes pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, piperazinyl, pyrazinyl, pyridazinyl, morpholinyl, azepanyl, azetidinyl, pyrrolidinyl or piperidinyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, OA, OH, Hal, CN and/or =O (carbonyl oxygen);

in Ig A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which 1-2 non-adjacent CH_2 groups may be replaced by O, NH, NMe or NEt, and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl,
or cyclic alkyl having 3-8 C atoms;

in Ih R^1 and R^2, together with the N atom to which they are bonded, denote an unsubstituted saturated, unsaturated or aromatic mono- or bicyclic heterocycle, which may contain a further 1 to 2 N, O and/or S atoms,

R^3, R^4 each, independently of one another, denote H, A, $(CH_2)_nCOHet$ or $(CH_2)_nC(=CH_2)CONR^5R^6$,

R^3 and R^4, together with the C atom to which they are bonded, also denote an unsubstituted saturated monocyclic C3-C6-

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carbocycle, which may contain a further 1 to 3 N, O and/or S atoms,

X denotes $CONR^5R^6$, $COOR^5$, $COHet^1$, Het^1, $CONH(CH_2)_pCN$ or $CONH(CH_2)_pNR^5R^6$,

Het denotes pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, piperazinyl, pyrazinyl, pyridazinyl, morpholinyl, azepanyl, azetidinyl, pyrrolidinyl or piperidinyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, OA, OH, Hal, CN and/or =O (carbonyl oxygen),

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which 1-2 non-adjacent CH_2 groups may be replaced by O, NH, NMe or NEt, and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl,
or cyclic alkyl having 3-8 C atoms,

Hal denotes F, Cl, Br or I,

n denotes 0, 1, 2, 3 or 4,

p denotes 1, 2, 3 or 4;

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

The compounds according to the invention and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use may also be made here of variants known per se which are not mentioned here in greater detail.

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If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds according to the invention.

The starting compounds are generally known. If they are novel, however, they can be prepared by methods known per se.

Compounds of the formula I can preferably be obtained by reacting a compound of the formula II with a compound of the formula III.

In the compounds of the formula II, R denotes an amino-protecting group, preferably tert-butyloxycarbonyl (BOC).

The reaction is carried out with addition of fluorides, preferably caesium fluoride.

The reaction is carried out by methods which are known to the person skilled in the art.

Reaction is initially carried out in a suitable solvent.

Examples of suitable solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

The solvent is particularly preferably acetonitrile or DMF.

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Depending on the conditions used, the reaction time is between a few minutes and 14 days, the reaction temperature is between about 0° and 150°, normally between 15° and 120°, particularly preferably between 20° and 60°C.

The term "amino-protecting group" is known in general terms and relates to groups which are suitable for protecting (blocking) an amino group against chemical reactions, but which are easily removable after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino-protecting groups are removed after the desired reaction (or reaction sequence), their type and size are, in addition, not crucial; however, preference is given to those having 1-20, in particular 1-8, C atoms. The term "acyl group" is to be understood in the broadest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and, in particular, alkoxycarbonyl, aryloxycarbonyl and especially aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl, such as acetyl, propionyl, butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl or toluyl; aryloxyalkanoyl, such as POA; alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC (tert.-butyloxycarbonyl), 2-iodoethoxycarbonyl; aralkoxycarbonyl, such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl, FMOC; arylsulfonyl, such as Mtr. Preferred amino-protecting groups are BOC and Mtr, furthermore CBZ, Fmoc, benzyl and acetyl.

The compounds of the formula I are liberated from their functional derivatives using - depending on the protecting group used - for example, strong acids, advantageously using TFA or perchloric acid, but also using other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids, such as trichloroacetic acid, or sulfonic acids,

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such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but is not always necessary. Suitable inert solvents are preferably organic, for example carboxylic acids, such as acetic acid, ethers, such as tetrahydrofuran or dioxane, amides, such as DMF, halogenated hydrocarbons, such as dichloromethane, furthermore also alcohols, such as methanol, ethanol or isopropanol, and water. Mixtures of the above-mentioned solvents are furthermore suitable. TFA is preferably used in excess without addition of a further solvent, perchloric acid in the form of a mixture of acetic acid and 70% perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are advantageously between about 0 and about 50°, work preferably being carried out between 15 and 30° (room temperature).

The BOC, OBut and Mtr groups can, for example, preferably be cleaved off using TFA in dichloromethane or using approximately 3 to 5N HCl in dioxane at 15-30°, the FMOC group using an approximately 5 to 50% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°.

Hydrogenolytically removable protecting groups (for example CBZ, benzyl or the liberation of the amidino group from the oxadiazole derivative thereof) can be cleaved off, for example, by treatment with hydrogen in the presence of a catalyst (for example a noble-metal catalyst, such as palladium, advantageously on a support, such as carbon). Suitable solvents here are those indicated above, in particular, for example, alcohols, such as methanol or ethanol, or amides, such as DMF. The hydrogenolysis is generally carried out at temperatures between about 0 and 100° and pressures between about 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group succeeds well, for example, on 5 to 10% Pd/C in methanol or using ammonium formate (instead of hydrogen) on Pd/C in methanol/DMF at 20-30°.

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It is furthermore possible to convert a compound of the formula I into another compound of the formula I by, for example, reducing nitro groups to amino groups, for example by hydrogenation on Raney nickel or Pd/carbon in an inert solvent, such as methanol or ethanol, and/or

converting an ester group into a carboxyl group or

esterifying carboxyl groups by reaction with alcohols and/or

converting carboxyl groups or acid chlorides into an acid amide by reaction with an amine.

Ester can be saponified, for example, using acetic acid or using NaOH or KOH in water, water/THF or water/dioxane at temperatures between 0 and 100°.

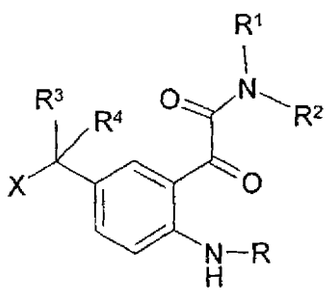
Furthermore, free amino and/or hydroxyl groups can be acylated in a conventional manner using an acid chloride or anhydride or alkylated using an unsubstituted or substituted alkyl halide, advantageously in an inert solvent, such as dichloromethane or THF, and/or in the presence of a base, such as triethylamine or pyridine, at temperatures between -60 and +30°.

Ether cleavages are carried out by methods which are known to the person skilled in the art.

The reaction is carried out in a suitable solvent, as indicated above, preferably by addition of boron tribromide.

The reaction is particularly preferably carried out in dichloromethane at a reaction temperature between about -30° and 50°, normally between -20° and 20°, in particular between about -15° and about 0°.

The invention also relates to the compounds of the formula II



II

in which

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R^1, R^2 each, independently of one another, denote H, A, $(CH_2)_nHet$ or $(CH_2)_nAr$,

R^1 and R^2, together with the N atom to which they are bonded, also denote a saturated, unsaturated or aromatic mono- or bicyclic heterocycle, which may contain a further 1 to 3 N, O and/or S atoms and which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nHet$, $(CH_2)_nAr$, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nNH_2$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, NHCOA, NA'COA, $CONH_2$, CONHA, CONAA', $OC(=O)(CH_2)_pNH_2$ and/or =O (carbonyl oxygen),

R^3, R^4 each, independently of one another, denote H, Hal, A, $(CH_2)_nHet$, $(CH_2)_nAr$, $(CH_2)_nCOHet$ or $(CH_2)_nC(=CH_2)CONR^5R^6$,

R^3 and R^4, together with the C atom to which they are bonded, also denote a saturated or unsaturated monocyclic C3-C10-carbocycle, which may contain a further 1 to 3 N, O and/or S atoms and which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nNH_2$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, NHCOA, NA'COA, $CONH_2$, CONHA, CONAA', $OC(=O)(CH_2)_pNH_2$ and/or =O (carbonyl oxygen),

R denotes tert-butyloxycarbonyl,

X denotes $COOR^5$,

R^5 denotes A,

Ar denotes phenyl, naphthyl, tetrahydronaphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, Hal, $(CH_2)_nOA$, $(CH_2)_nOH$, $(CH_2)_nCN$, SA, SOA, SO_2A, NO_2, C≡CH, $(CH_2)_nCOOH$, CHO, $(CH_2)_nCOOA$, $CONH_2$, CONHA, CONAA', NHCOA, CH(OH)A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNAA'$, $(CH_2)_nNHSO_2A$, $SO_2NH(CH_2)_nNH_2$, SO_2NH_2, SO_2NHA, SO_2NAA', $CONH(CH_2)_nCOOA$, $CONH(CH_2)_nCOOH$, $NHCO(CH_2)_nCOOA$, $NHCO(CH_2)_nCOOH$, $CONH(CH_2)_nNH_2$, $CONH(CH_2)_nNHA$, $CONH(CH_2)_nNAA'$, $CONH(CH_2)_nCN$ and/or $(CH_2)_nCH(NH_2)COOH$,

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	Het	denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, OA, OH, phenyl, SH, $S(O)_mA$, Hal, NO_2, CN, COA, COOA, COObenzyl, $CONH_2$, CONHA, CONAA', SO_2NH_2, NH_2, NHA, NAA', NHCOA, $NHSO_2A$ and/or =O (carbonyl oxygen),
	A, A'	each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which 1-3 non-adjacent CH_2 groups may be replaced by O, S, SO, SO_2, NH, NMe or NEt, and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl, or cyclic alkyl having 3-8 C atoms,
	Hal	denotes F, Cl, Br or I,
	n	denotes 0, 1, 2, 3 or 4,
	p	denotes 1, 2, 3 or 4,

and salts thereof.

The meanings and the preferred meanings of the radicals indicated are those as indicated above for the compounds of the formula I.

Pharmaceutical salts and other forms

The said compounds according to the invention can be used in their final non-salt form. On the other hand, the present invention also encompasses the use of these compounds in the form of their pharmaceutically acceptable salts, which can be derived from various organic and inorganic acids and bases by procedures known in the art. Pharmaceutically acceptable salt forms of the compounds according to the invention are for the most part prepared by conventional methods. If the compound according to the invention contains a carboxyl group, one of its suitable salts can be formed by reacting the compound with a suitable base to give the corresponding base-addition salt. Such bases are, for example, alkali metal hydroxides, including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline-earth metal hydroxides, such as barium hydroxide and calcium hydroxide;

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alkali metal alkoxides, for example potassium ethoxide and sodium propoxide; and various organic bases, such as piperidine, diethanolamine and N-methylglutamine. The aluminium salts of the compounds of the formula I are likewise included. In the case of certain compounds of the formula I, acid-addition salts can be formed by treating these compounds with pharmaceutically acceptable organic and inorganic acids, for example hydrogen halides, such as hydrogen chloride, hydrogen bromide or hydrogen iodide, other mineral acids and corresponding salts thereof, such as sulfate, nitrate or phosphate and the like, and alkyl- and monoarylsulfonates, such as ethanesulfonate, toluenesulfonate and benzenesulfonate, and other organic acids and corresponding salts thereof, such as acetate, trifluoroacetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate and the like. Accordingly, pharmaceutically acceptable acid-addition salts of the compounds of the formula I include the following: acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, palmoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate, but this does not represent a restriction.

Furthermore, the base salts of the compounds according to the invention include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zinc salts, but this is not intended to represent a restriction. Of the above-men-

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tioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline-earth metal salts calcium and magnesium. Salts of the compounds according to the invention which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris(hydroxymethyl)methylamine (tromethamine), but this is not intended to represent a restriction.

Compounds of the present invention which contain basic nitrogen-containing groups can be quaternised using agents such as (C_1-C_4)alkyl halides, for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and iodide; di(C_1-C_4)alkyl sulfates, for example dimethyl, diethyl and diamyl sulfate; (C_{10}-C_{18})alkyl halides, for example decyl, dodecyl, lauryl, myristyl and stearyl chloride, bromide and iodide; and aryl(C_1-C_4)alkyl halides, for example benzyl chloride and phenethyl bromide. Both water- and oil-soluble compounds according to the invention can be prepared using such salts.

The above-mentioned pharmaceutical salts which are preferred include acetate, trifluoroacetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stea-

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rate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate and tromethamine, but this is not intended to represent a restriction.

The acid-addition salts of basic compounds according to the invention are prepared by bringing the free base form into contact with a sufficient amount of the desired acid, causing the formation of the salt in a conventional manner. The free base can be regenerated by bringing the salt form into contact with a base and isolating the free base in a conventional manner. The free base forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free base forms thereof.

As mentioned, the pharmaceutically acceptable base-addition salts of the compounds according to the invention are formed with metals or amines, such as alkali metals and alkaline-earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of acidic compounds according to the invention are prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner. The free acid forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

If a compound according to the invention contains more than one group which is capable of forming pharmaceutically acceptable salts of this type,

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the invention also encompasses multiple salts. Typical multiple salt forms include, for example, bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium and trihydrochloride, but this is not intended to represent a restriction.

With regard to that stated above, it can be seen that the expression "pharmaceutically acceptable salt" in the present connection is taken to mean an active ingredient which comprises a compound according to the invention in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

Compounds according to the invention may be chiral owing to their molecular structure and may accordingly occur in various enantiomeric forms. They can therefore exist in racemic or in optically active form.

Since the pharmaceutical activity of the racemates or stereoisomers of the compounds according to the invention may differ, it may be desirable to use the enantiomers. In these cases, the end product or even the intermediates can be separated into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or even employed as such in the synthesis.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid,

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malic acid, lactic acid, suitably N-protected amino acids (for example N-benzoylproline or N-benzenesulfonylproline), or the various optically active camphorsulfonic acids. Also advantageous is chromatographic enantiomer resolution with the aid of an optically active resolving agent (for example dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatised methacrylate polymers immobilised on silica gel). Suitable eluents for this purpose are aqueous or alcoholic solvent mixtures, such as, for example, hexane/isopropanol/ acetonitrile, for example in the ratio 82:15:3.

The invention furthermore relates to the use of the compounds and/or physiologically acceptable salts thereof for the preparation of a medicament (pharmaceutical composition), in particular by non-chemical methods. They can be converted into a suitable dosage form here together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and, if desired, in combination with one or more further active ingredients.

The invention furthermore relates to medicaments comprising at least one compound according to the invention and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

Pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Such a unit can comprise, for example, 0.1 mg to 3 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the condition treated, the method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Preferred dosage unit formulations are those which comprise a daily

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dose or part-dose, as indicated above, or a corresponding fraction thereof of an active ingredient. Furthermore, pharmaceutical formulations of this type can be prepared using a process which is generally known in the pharmaceutical art.

Pharmaceutical formulations can be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can be prepared using all processes known in the pharmaceutical art by, for example, combining the active ingredient with the excipient(s) or adjuvant(s).

Pharmaceutical formulations adapted for oral administration can be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Thus, for example, in the case of oral administration in the form of a tablet or capsule, the active-ingredient component can be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

Capsules are produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, calcium stearate or polyethylene glycol in solid form, can be added to the pow-

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der mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, may likewise be added in order to improve the availability of the medicament after the capsule has been taken.

In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture. Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the like. The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinylpyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbent, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acadia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture can be run through a tabletting machine, giving lumps of non-uniform shape which are broken up to form granules. The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds. The lubricated mixture is then pressed to give tablets. The compounds according to the

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invention can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the granulation or dry-pressing steps. A transparent or opaque protective layer consisting of a shellac sealing layer, a layer of sugar or polymer material and a gloss layer of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

Oral liquids, such as, for example, solution, syrups and elixirs, can be prepared in the form of dosage units so that a given quantity comprises a pre-specified amount of the compound. Syrups can be prepared by dissolving the compound in an aqueous solution with a suitable flavour, while elixirs are prepared using a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersion of the compound in a non-toxic vehicle. Solubilisers and emulsifiers, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavour additives, such as, for example, peppermint oil or natural sweeteners or saccharin, or other artificial sweeteners and the like, can likewise be added.

The dosage unit formulations for oral administration can, if desired, be encapsulated in microcapsules. The formulation can also be prepared in such a way that the release is extended or retarded, such as, for example, by coating or embedding of particulate material in polymers, wax and the like.

The compounds according to the invention and salts, solvates and physiologically functional derivatives thereof can also be administered in the form of liposome delivery systems, such as, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

The compounds according to the invention and the salts, solvates and physiologically functional derivatives thereof can also be delivered using

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monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds can also be coupled to soluble polymers as targeted medicament carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds may furthermore be coupled to a class of biodegradable polymers which are suitable for achieving controlled release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydroxypyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration can be administered as independent plasters for extended, close contact with the epidermis of the recipient. Thus, for example, the active ingredient can be delivered from the plaster by iontophoresis, as described in general terms in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compounds adapted for topical administration can be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For the treatment of the eye or other external tissue, for example mouth and skin, the formulations are preferably applied as topical ointment or cream. In the case of formulation to give an ointment, the active ingredient can be employed either with a paraffinic or a water-miscible cream base. Alternatively, the active ingredient can be formulated to give a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical application to the eye include eye drops, in which the active ingredient is dissolved or suspended in a suitable carrier, in particular an aqueous solvent.

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Pharmaceutical formulations adapted for topical application in the mouth encompass lozenges, pastilles and mouthwashes.

Pharmaceutical formulations adapted for rectal administration can be administered in the form of suppositories or enemas.

Pharmaceutical formulations adapted for nasal administration in which the carrier substance is a solid comprise a coarse powder having a particle size, for example, in the range 20-500 microns, which is administered in the manner in which snuff is taken, i.e. by rapid inhalation via the nasal passages from a container containing the powder held close to the nose. Suitable formulations for administration as nasal spray or nose drops with a liquid as carrier substance encompass active-ingredient solutions in water or oil.

Pharmaceutical formulations adapted for administration by inhalation encompass finely particulate dusts or mists, which can be generated by various types of pressurised dispensers with aerosols, nebulisers or insufflators.

Pharmaceutical formulations adapted for vaginal administration can be administered as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood of the recipient to be treated; and aqueous and non-aqueous sterile suspensions, which may comprise suspension media and thickeners. The formulations can be administered in single-dose or multidose containers, for example sealed ampoules and

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vials, and stored in freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary.

Injection solutions and suspensions prepared in accordance with the recipe can be prepared from sterile powders, granules and tablets.

It goes without saying that, in addition to the above particularly mentioned constituents, the formulations may also comprise other agents usual in the art with respect to the particular type of formulation; thus, for example, formulations which are suitable for oral administration may comprise flavours.

A therapeutically effective amount of a compound of the present invention depends on a number of factors, including, for example, the age and weight of the human or animal, the precise condition requiring treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately determined by the treating doctor or vet. However, an effective amount of a compound according to the invention for the treatment is generally in the range from 0.1 to 100 mg/kg of body weight of the recipient (mammal) per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus, the actual amount per day for an adult mammal weighing 70 kg is usually between 70 and 700 mg, where this amount can be administered as an individual dose per day or usually in a series of part-doses (such as, for example, two, three, four, five or six) per day, so that the total daily dose is the same. An effective amount of a salt or solvate or of a physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound according to the invention *per se*. It can be assumed that similar doses are suitable for the treatment of other conditions mentioned above.

The invention furthermore relates to medicaments comprising at least one compound according to the invention and/or pharmaceutically usable deri-

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vatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

Further medicament active ingredients are preferably chemotherapeutic agents, in particular those which inhibit angiogenesis and thus inhibit the growth and spread of tumour cells; preference is given here to VEGF receptor inhibitors, including robozymes and antisense which are directed to VEGF receptors, and angiostatin and endostatin.

Examples of antineoplastic agents which can be used in combination with the compounds according to the invention generally include alkylating agents, antimetabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazin; mitoxantron or platinum coordination complexes.

Antineoplastic agents are preferably selected from the following classes: anthracyclins, vinca medicaments, mitomycins, bleomycins, cytotoxic nucleosides, epothilones, discodermolides, pteridines, diynenes and podophyllotoxins.

Particular preference is given in the said classes to, for example, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloromethotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosinarabinoside, podophyllotoxin or podophyllotoxin derivatives, such as, for example, etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine and paclitaxel. Other preferred antineoplastic agents are selected from the group estramustine, carboplatin, cyclophosphamide, bleomycin, gemcitabine, ifosamide, melphalan, hexamethylmelamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, arabinosylcytosine, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins.

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The invention also relates to a set (kit) consisting of separate packs of

(a) an effective amount of a compound according to the invention and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
and

(b) an effective amount of a further medicament active ingredient.

The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules, each containing an effective amount of a compound according to the invention and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
and an effective amount of a further medicament active ingredient in dissolved or lyophilised form.

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The present compounds are suitable as pharmaceutical active ingredients for mammals, in particular for humans, in the treatment of diseases in which HSP90 plays a role.

The invention thus relates to the use of the compounds according to the invention, and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of diseases in which the inhibition, regulation and/or modulation of HSP90 plays a role.

The present invention encompasses the use of the compounds according to the invention and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of tumour diseases, such as, for example, fibrosarcoma, myxosarcoma, liposarcoma, chondro-

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sarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumour, leiosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, syringocarcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinomas, bone marrow carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonic carcinoma, Wilm's tumour, cervical cancer, testicular tumour, lung carcinoma, small-cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, haemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukaemia, lymphoma, multiple myeloma, Waldenström's macroglobulinaemia and heavy chain disease;

viral diseases, where the viral pathogen is selected from the group consisting of hepatitis type A, hepatitis type B, hepatitis type C, influenza, varicella, adenovirus, herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), cattle plague, rhinovirus, echovirus, rotavirus, respiratory syncytial virus (RSV), papillomavirus, papovavirus, cytomegalovirus, echinovirus, arbovirus, huntavirus, Coxsackie virus, mumps virus, measles virus, rubella virus, polio virus, human immunodeficiency virus type I (HIV-I) and human immunodeficiency virus type II (HIV-II);

for immune suppression in transplants; inflammation-induced diseases, such as rheumatoid arthritis, asthma, sepsis, multiple sclerosis, type 1 diabetes, lupus erythematosus, psoriasis and inflammatory bowel disease; cystic fibrosis; diseases associated with angiogenesis, such as, for example, diabetic retinopathy, haemangiomas, endometriosis, tumour angiogenesis; infectious diseases; autoimmune diseases; ischaemia; promotion of nerve regeneration; fibrogenetic diseases, such as, for example, scleroderma, polymyositis, systemic lupus, cirrhosis of the liver, keloid formation, interstitial nephritis and pulmonary fibrosis;

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The compounds according to the invention can inhibit, in particular, the growth of cancer, tumour cells and tumour metastases and are therefore suitable for tumour therapy.

The present invention furthermore encompasses the use of the compounds according to the invention and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the protection of normal cells against toxicity caused by chemotherapy, and for the treatment of diseases in which incorrect protein folding or aggregation is a principal causal factor, such as, for example, scrapie, Creutzfeldt-Jakob disease, Huntington's or Alzheimer's.

The invention also relates to the use of the compounds according to the invention and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of diseases of the central nervous system, of cardiovascular diseases and cachexia.

In a further embodiment, the invention also relates to the use of the compounds according to the invention and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for HSP90 modulation, where the modulated biological HSP90 activity causes an immune reaction in an individual, protein transport from the endoplasmatic reticulum, recovery from hypoxic/anoxic stress, recovery from malnutrition, recovery from heat stress, or combinations thereof, and/or where the disorder is a type of cancer, an infectious disease, a disorder associated with disrupted protein transport from the endoplasmatic reticulum, a disorder associated with ischaemia/reperfusion, or combinations thereof, where the the disorder associated with ischaemia/reperfusion is a consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke,

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cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress.

In a further embodiment, the invention also relates to the use of the compounds according to the invention and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of ischaemia as a consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress.

Test method for the measurement of HSP90 inhibitors

The binding of geldanamycin or 17- allylamino-17-demethoxygeldanamycin (17AAG) to HSP90 and competitive inhibition thereof can be utilised in order to determine the inhibitory activity of the compounds according to the invention (Carreras et al. 2003, Chiosis et al. 2002).
In the specific case, a radioligand filter binding test is used. The radioligand used here is tritium-labelled 17-allylaminogeldanamycin, [3H]17AAG. This filter binding test allows a targeted search for inhibitors which interfere with the ATP binding site.

Material

Recombinant human HSP90α (E. coli expressed, 95% purity);

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[3H]17AAG (17-allylaminogeldanamycin, [allylamino-2,3-^{3}H. Specific activity: 1.11x10^{12} Bq/mmol (Moravek, MT-1717);
HEPES filter buffer (50 mM HEPES, pH 7.0, 5 mM MgCl2, BSA 0.01%)
Multiscreen FB (1 µm) filter plate (Millipore, MAFBNOB 50).

Method

The 96-well microtitre filter plates are firstly irrigated and coated with 0.1% of polyethylenimine.

The test is carried out under the following conditions:

Reaction temperature 22°C

Reaction time: 30 min., shaking at 800 rpm
Test volume: 50 µl
Final concentrations:
50 mM HEPES HCl, pH 7.0, 5 mM MgCl2, 0.01% (w/v) of BSA
HSP90: 1.5 µg/assay
[3H]17AAG: 0.08 µM.

At the end of the reaction, the supernatant in the filter plate is removed by suction with the aid of a vacuum manifold (Multiscreen Separation System, Millipore), and the filter is washed twice.
The filter plates are then measured in a beta counter (Microbeta, Wallac) with scintillator (Microscint 20, Packard).

"% of control" is determined from the "counts per minutes" values, and the IC-50 value of a compound is calculated therefrom.

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Table I

HSP90 inhibition by compounds of the formula I according to the invention

Compound No.	IC_{50}	Compound No.	IC_{50}
"A1"	A	"A21"	A
"A2"	B	"A22"	B
"A3"	B	"A23"	B
"A4"	A	"A24"	B
"A5"	A	"A25"	B
"A6"	B	"A26"	B
"A7"	B	"A27"	B
"A8"	B	"A28"	B
"A9"	B	"A29"	A
"A10"	B	"A30"	A
"A11"	B	"A31"	A
"A12"	B	"A32"	A
"A13"	B	"A33"	A
"A14"	B	"A34"	A
"A15"	B	"A35"	A
"A16"	B	"A36"	A
"A17"	B	"A37"	A
"A18"	C	"A38"	A
"A19"	B	"A39"	A
"A20"	A	"A40"	B

Compound No	IC_{50}	Compound No.	IC_{50}
"A41"	A	"A61"	
"A42"	B	"A62"	
"A43"	A	"A63"	
"A44"	A	"A64"	
"A45"	A	"A65"	

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"A46"	A	"A66"	
"A47"	A	"A67"	
"A48"	A	"A68"	
"A49"		"A69"	
"A50"	B	"A70"	
"A51"		"A71"	
"A52"		"A72"	
"A53"	A	"A73"	
"A54"	B	"A74"	B
"A55"	A	"A75"	
"A56"	A	"A76"	B
"A57"	A	"A77"	
"			
"A59"			
"A60"			

IC_{50}: 10 nM - 1 μM = A

1 μM - 10 μM = B

> 10 μM = C

Above and below, all temperatures are indicated in °C. In the following examples, "conventional work-up" means: water is added if necessary, the pH is adjusted, if necessary, to values between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation.

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LC-MS conditions

The LC/MS measurements are carried out using a Hewlett Packard HP 1200 series system having the following features: ion source: electrospray (positive mode); scan: 100-1000 m/e; fragmentation voltage: 60 V; gas temperature: 300°C, UV: 220 nm.

Flow rate: 2.4 ml/min.

Column: Chromolith SpeedROD RP-18e 50-4.6

Solvent: LiChrosolv grade from Merck KGaA

Solvent A: H2O (0.05% of formic acid)

Solvent B: ACN (0.04% of formic acid)

"Standard" gradient:

4% of B → 100% of B: 0 min to 2.8 min

100% of B: 2.8 min to 3.3 min

100% of B → 4% of B: 3.3 min to 3.4 min

"Polar" gradient:

1% of B → 100% of B: 0 min to 3.5 min

100% of B: 3.5 min to 5 min

100% of B → 10% of B: 5 min to 5.5 min

10% of B → 1% of B: 5.5 min to 6 min

"Nonpolar" gradient:

20% of B → 100% of B: 0 min to 2.8 min

100% of B: 2.8 min to 3.3 min

100% of B → 20% of B: 3.3 min to 3.4 min

If no further information is provided regarding the retention time, "standard" gradient is used.

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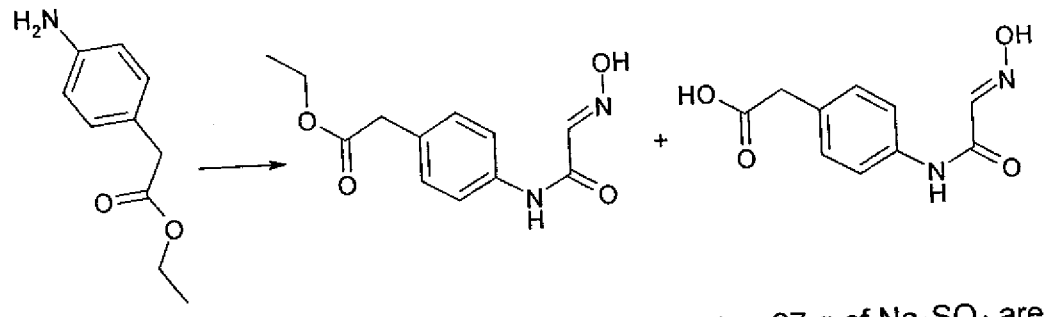
Example 1

Preparation of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetate ("A1") and 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetic acid ("A2")

Step 1: Ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenylacetate



18 g of chloral hydrate are dissolved in 100 ml of water, 27 g of Na_2SO_4 are added, and the mixture is stirred at 23°C for 10 min. A solution of 20 g of ethyl 4-aminophenylacetate hydrochloride in 100 ml of water is added to this solution. 19 g of hydroxylammonium chloride in 50 ml of water are added to the resultant suspension, and the mixture is stirred at 60°C for 90 min. The mixture is subsequently allowed to cool, during which a precipitate deposits. This is filtered off, washed with water and dried at 40°C in vacuo. The mixture obtained was employed in the following reaction without further purification.

Yield: 11.2 g (mixture of ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]-phenylacetate and 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenylacetic acid in the ratio 1 : 1.7);

LC-MS retention time: 1.22 min (ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]-amino]phenylacetate) and 0.51 min (2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]-amino]phenylacetic acid).

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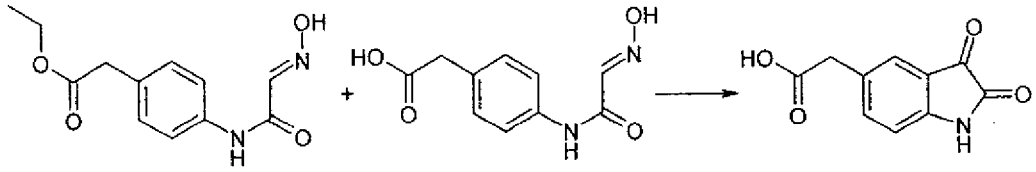
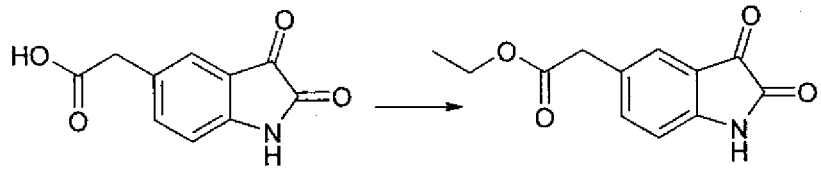
Step 2: (2,3-Dioxo-2,3-dihydro-1H-indol-5-yl)acetic acid



11.6 g of the mixture obtained from step 1 are added in portions to 30 ml of sulfuric acid (98%) at 50°C, during which the temperature rises to 120°C. When the addition is complete, the mixture is stirred for a further 15 min and subsequently poured into 400 ml of ice-water. The resultant precipitate is filtered off, washed with water. Drying at 40°C in vacuo gives 8.1 g of (2,3-dioxo-2,3-dihydro-1H-indol-5-yl)acetic acid; LC-MS retention time: 1.11 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.48 (dd, J = 8.0, 1.8, 1H), 7.42 (d, J = 1.2, 1H), 6.88 (d, J = 8.0, 1H), 3.59 (s, 2H).

Step 3: Ethyl 2-(2,3-dioxoindolin-5-yl)acetate



4 g of (2,3-dioxo-2,3-dihydro-1H-indol-5-yl)acetic acid are dissolved in 100 ml of ethanol, and 300 mg of toluene-4-sulfonic acid monohydrate are added. The mixture is heated at 80°C for 1 h, and the solvent is subsequently removed in vacuo. The residue is taken up in 100 ml of water and 100 ml of ethyl acetate and stirred at 60°C for a further 12 h. The mixture is neutralised using sodium hydrogencarbonate, and the organic phase is separated off. The aqueous phase is washed a further twice with 100 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate, filtered and evaporated to dryness in vacuo, giving 4.1 g of ethyl 2-(2,3-dioxoindolin-5-yl)acetate; LC-MS retention time: 1.09 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.46 (dd, J = 8.1, 1.8, 1H), 7.40 (d, J = 1.2, 1H), 6.87 (d, J = 7.9, 1H), 4.06 (q, J = 7.2, 2H), 3.63 (s, 2H), 1.17 (t, J = 7.1, 3H).

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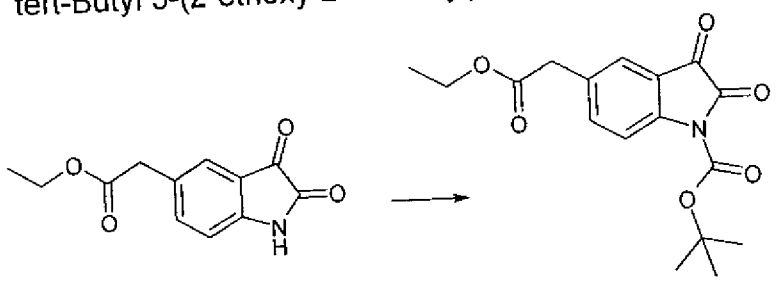
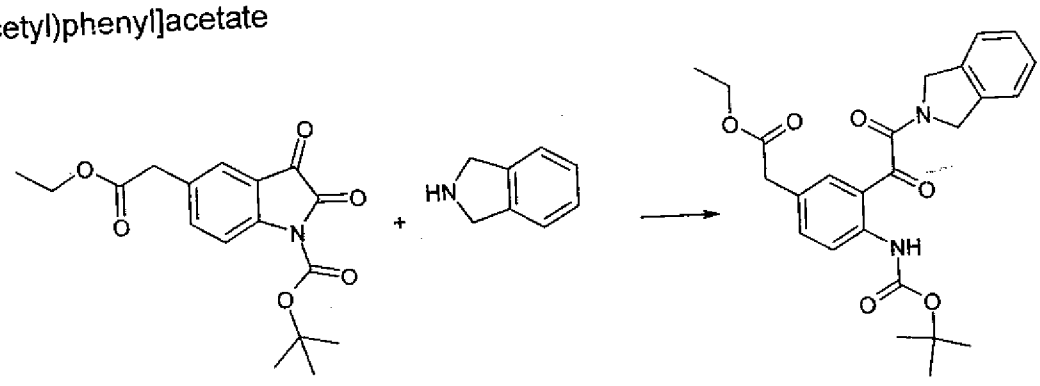
Step 4: tert-Butyl 5-(2-ethoxy-2-oxoethyl)-2,3-dioxoindoline-1-carboxylate



520 mg of di-tert-butyl dicarbonate are added to 549 mg of ethyl 2-(2,3-dioxoindolin-5-yl)acetate and 15 mg of 4-dimethylaminopyridine in 20 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 12 h. The solvent is removed at 23°C in vacuo, and the product is processed further directly;

LC-MS retention time: 2.02 min ("nonpolar" gradient).

Step 5: Ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]acetate



2.2 g of isoindoline are added to 5.9 g of tert-butyl 5-(2-ethoxy-2-oxoethyl)-2,3-dioxoindoline-1-carboxylate in 100 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 1 h. The solvent is removed in vacuo, and the residue is purified by column chromatography, giving 4.9 g of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxoacetyl)phenyl]acetate;

LC-MS retention time: 2.50 min ("nonpolar" gradient).

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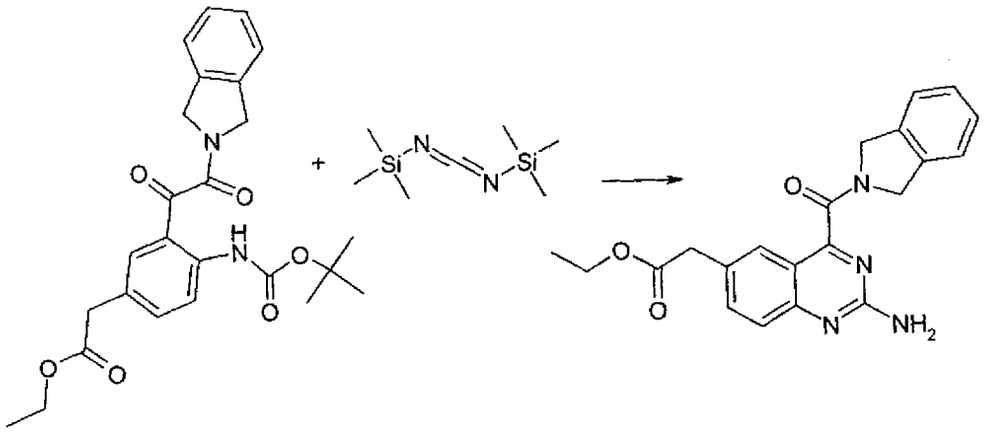
Step 6: Ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl] acetate ("A1")



4.9 g of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]acetate are dissolved in 100 ml of acetonitrile under argon. 1.7 g of caesium fluoride are added, and 3 ml of bis(trimethylsilyl)carbodiimide are added dropwise to the solution over the course of 5 min. The mixture is stirred at room temperature for 15 min, and 20 ml of dichloromethane are then added. After addition of 20 ml of hydrochloric acid (1N), the product precipitates out as white solid.

Yield: 2.8 g (69%) of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-ylacetate;

LC-MS retention time: 1.49 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.95 (dd, J = 10.7, 1.9, 2H), 7.72 (d, J = 8.6, 1H), 7.43 (d, J = 7.5, 1H), 7.29 (dt, J = 23.7, 7.3, 2H), 7.20 (d, J = 7.3, 1H), 5.02 (s, 2H), 4.75 (s, 2H), 4.05 (q, J = 7.1, 2H), 3.83 (s, 2H), 1.13 (t, J = 7.1, 3H).

Step 7: 2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetic acid ("A2")

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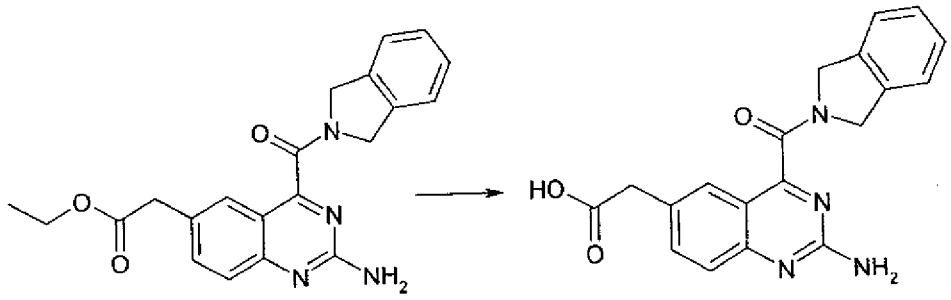


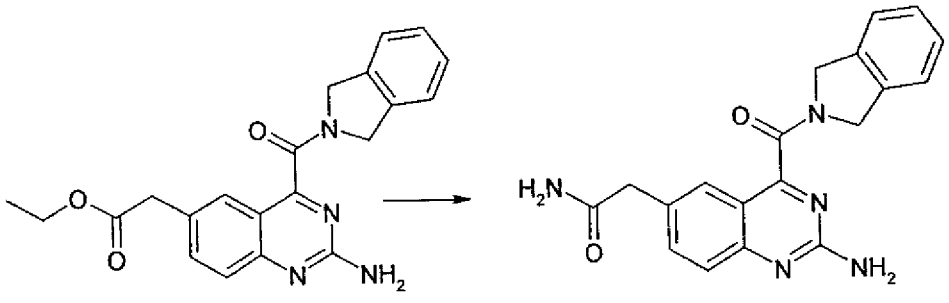
2.7 g of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetate are dissolved in 40 ml of tetrahydrofuran, and 25 ml of 2N sodium hydroxide solution are added. The mixture is stirred at 23°C for 12 h, evaporated to dryness in vacuo, taken up in 10 ml of water and adjusted to pH 2 using 7 ml of 25% hydrochloric acid. The resultant precipitate is filtered off and dried in vacuo. Yield: 2.0 g (80%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-acetic acid;

LC-MS retention time: 1.04 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.96 (d, J = 7.0, 2H), 7.74 – 7.69 (m, 1H), 7.44 (d, J = 7.5, 1H), 7.30 (dt, J = 23.5, 7.3, 2H), 7.21 (d, J = 7.3, 1H), 5.02 (s, 2H), 4.76 (s, 2H), 3.76 (s, 2H).

Example 2

Preparation of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetamide ("A3")



100 mg of "A1" are dissolved in 40 ml of methanol, and 135 mg of magnesium nitride are added. The mixture is stirred at 80°C for 12 h, cooled, diluted with 10 ml of water and adjusted to pH 2 using 25% hydrochloric acid. The resultant precipitate is filtered off and purified by column chromatography. Yield:

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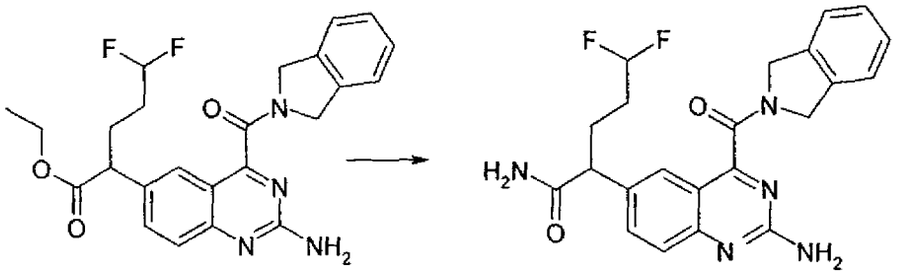
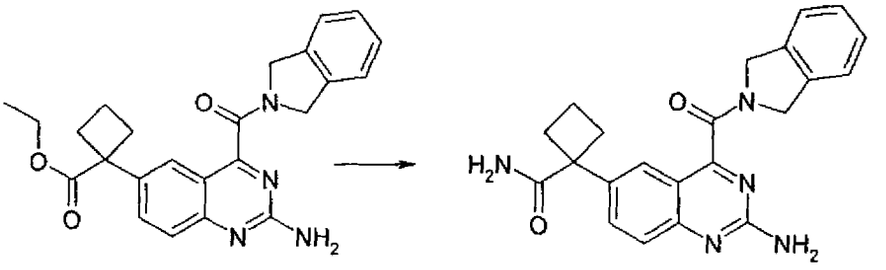
18 mg (20%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetamide; LC-MS retention time: 0.74 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.98 (dd, J = 8.7, 1.8, 1H), 7.93 (d, J = 1.4, 1H), 7.73 (d, J = 8.5, 1H), 7.48 (d, J = 7.3, 1H), 7.34 (dt, J = 17.9, 6.9, 2H), 7.25 (d, J = 7.3, 1H), 5.05 (s, 2H), 4.80 (s, 2H), 3.58 (s, 2H).

The compound 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5,5-difluoropentanamide ("A4") is obtained analogously



Yield: 15 mg (16%); LC-MS retention time: 1.64 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] (dd, J = 8.9, 1.9, 1H), 7.64 (d, J = 1.8, 1H), 7.52 – 7.42 (m, 2H), 7.36 – 7.23 (m, 3H), 7.00 (s, 2H), 6.03 (tt, J = 57.0, 4.1, 1H), 4.99 (s, 2H), 4.67 (s, 2H), 3.52 (dd, J = 8.5, 6.0, 1H), 2.09 – 1.56 (m, 4H).

The compound 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclobutanecarboxamide ("A5") is obtained analogously



Yield: 9 mg (10%); LC-MS retention time: 1.12 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.03 (dd, J = 8.7, 2.0, 1H), 7.99 (d, J = 1.7, 1H), 7.78 (d, J = 8.7, 1H), 7.48 (d, J = 7.0, 1H), 7.40 – 7.29

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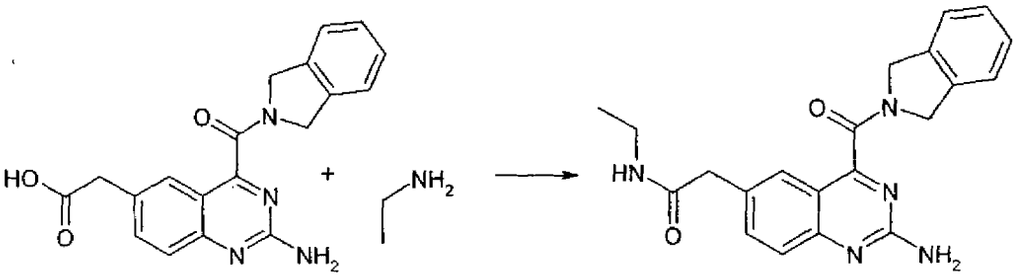
(m, 2H), 7.27 (d, J = 7.6, 1H), 5.10 (s, 2H), 4.86 (s, 2H), 2.84 – 2.73 (m, 2H), 2.45 – 2.37 (m, 2H), 1.97 – 1.69 (m, 2H).

Example 3

Preparation of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-acetamide ("A6")



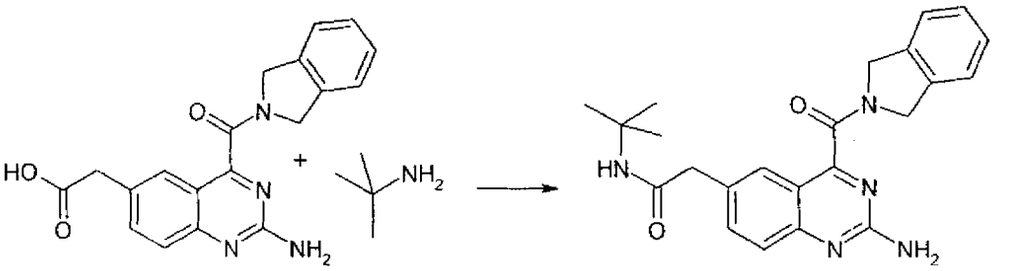
50 mg of "A2" are dissolved in 2 ml of ethylamine and irradiated in the microwave (CEM Discover®) at max. 120°C for 60 min. The mixture is evaporated to dryness in vacuo, the residue is taken up in DMSO and purified by column chromatography. Yield: 8 mg (16%) of 2-[2-amino-4-(isoindoline-2-carbonyl)-quinazolin-6-yl]-N-ethylacetamide;

LC-MS retention time: 1.53 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.99 (dd, J = 8.6, 1.8, 1H), 7.95 (d, J = 1.2, 1H), 7.75 (d, J = 8.5, 1H), 7.48 (d, J = 7.2, 1H), 7.34 (dt, J = 18.6, 6.9, 2H), 7.25 (d, J = 7.3, 1H), 5.07 (s, 2H), 4.81 (s, 2H), 3.59 (s, 2H), 3.07 (q, J = 7.2, 2H), 0.99 (t, J = 7.2, 3H)

Example 4

Preparation of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-tert-butylacetamide ("A7")



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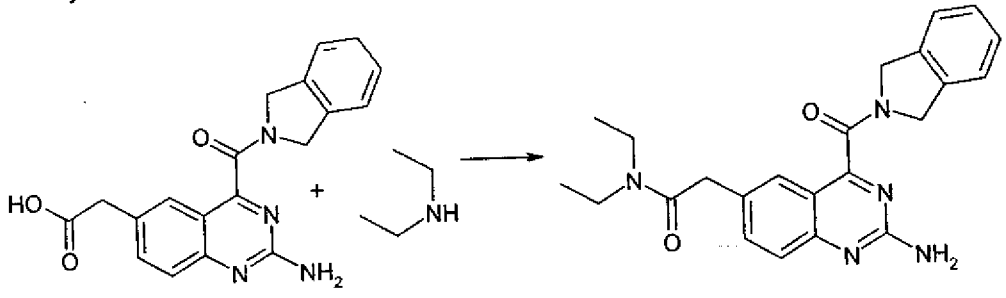
100 mg of "A2" are suspended in 3 ml of thionyl chloride and stirred at 23°C for 12 h. The mixture is evaporated to dryness in vacuo, and the residue is taken up in 4 ml of tetrahydrofuran. This solution is added to a solution of 35 µl of tert-butylamine and 46 µl of N-ethyldiisopropylamine in 2 ml of tetrahydrofuran. After 2 h at 23°C, the mixture is evaporated to dryness in vacuo, taken up in acetonitrile and purified by column chromatography. Yield: 32 mg (29%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-tert-butylacetamide; LC-MS retention time: 1.77 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.98 (dd, J = 8.6, 1.8, 1H), 7.93 (d, J = 1.3, 1H), 7.75 (d, J = 8.6, 1H), 7.48 (d, J = 7.5, 1H), 7.34 (dt, J = 24.0, 7.2, 2H), 7.24 (d, J = 7.5, 1H), 5.07 (s, 2H), 4.79 (s, 2H), 3.55 (s, 2H), 1.20 (s, 9H).

Example 5

Preparation of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N,N-diethylacetamide ("A8")



119.7 mg of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), 44.4 µl of diethylamine and 157.8 µl of 4-methylmorpholine are added to a solution of 100 mg of "A2" in 1 ml of dimethylformamide. The mixture is subsequently stirred at 25°C for 12 h. The mixture is evaporated to dryness in vacuo, taken up in 1 ml of dimethyl sulfoxide and purified by chromatography (reversed phase HPLC).

Yield: 60 mg (52%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N,N-diethylacetamide; LC-MS retention time: 1.76 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.94 (dd, J = 8.7, 1.7, 1H), 7.90 (s, 1H), 7.73 (d, J = 8.6, 1H), 7.48 (d, J = 7.5, 1H), 7.34 (dt, J = 23.3, 7.3,

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2H), 7.25 (d, J = 7.5, 1H), 5.05 (s, 2H), 4.78 (s, 2H), 3.88 (s, 2H), 3.38 (q, J = 7.1, 2H), 3.28 (q, J = 7.0, 2H), 1.13 (t, J = 7.2, 3H), 1.00 (t, J = 7.1, 3H).

The following compounds are obtained analogously:

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N,N-dimethylacetamide ("A9");
LC-MS retention time: 1.50 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.89 – 7.84 (m, 2H), 7.71 – 7.67 (m, 1H), 7.41 (d, J = 7.5, 1H), 7.28 (dt, J = 23.5, 7.2, 2H), 7.19 (d, J = 7.5, 1H), 5.01 (s, 2H), 4.75 (s, 2H), 3.84 (s, 2H), 3.00 (s, 3H), 2.79 (s, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-N-methylacetamide ("A10");
LC-MS retention time: 1.59 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] δ 7.89 – 7.83 (m, 2H), 7.68 (dd, J = 8.7, 2.5, 1H), 7.39 (d, J = 7.5, 1H), 7.27 (dt, J = 23.5, 7.2, 2H), 7.17 (d, J = 7.3, 1H), 5.00 (s, 2H), 4.74 (s, 2H), 3.87 – 3.76 (m, 2H), 3.40 – 3.23 (m, 2H), 2.96 – 2.73 (m, 3H), 1.10 – 0.89 (m, 3H); rotational isomer mixture.

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N-(2-hydroxyethyl)-N-methylacetamide ("A11");
LC-MS retention time: 1.38 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.92 – 7.82 (m, 2H), 7.70 (d, J = 8.6, 1H), 7.43 (d, J = 7.5, 1H), 7.30 (dt, J = 23.1, 7.4, 2H), 7.21 (d, J = 7.3, 1H), 5.01 (s, 2H), 4.76 (s, 2H), 3.96 – 3.84 (m, 2H), 3.54 (t, J = 5.6, 2H), 3.44 (t, J = 6.7, 2H), 3.32 – 3.29 (m, 2H), 1.12 – 0.93 (m, 3H); rotational isomer mixture.

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-hydroxyethyl)-N-ethylacetamide ("A12");
LC-MS retention time: 1.46 min;

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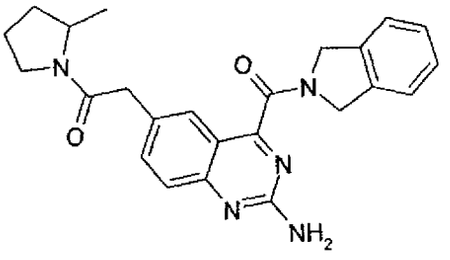
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.92 – 7.82 (m, 2H), 7.70 (d, J = 8.6, 1H), 7.43 (d, J = 7.5, 1H), 7.30 (dt, J = 23.1, 7.4, 2H), 7.21 (d, J = 7.3, 1H), 5.01 (s, 2H), 4.76 (s, 2H), 3.96 – 3.84 (m, 2H), 3.54 (t, J = 5.6, 2H), 3.44 (t, J = 6.7, 2H), 3.32 – 3.29 (m, 2H), 1.12 – 0.93 (m, 3H); rotational isomer mixture.

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N-(2-dimethylamino-ethyl)-N-ethylacetamide ("A59");
LC-MS retention time: 1.26 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.99 – 7.91 (m, 2H), 7.76 (d, J = 8.6, 1H), 7.47 (d, J = 7.5, 1H), 7.34 (dt, J = 23.5, 7.2, 2H), 7.25 (d, J = 7.5, 1H), 5.07 (s, 2H), 4.81 (s, 2H), 3.96 (s, 2H), 3.63 (t, J = 6.4, 2H), 3.48 (q, J = 7.0, 2H), 3.25 (t, J = 6.5, 2H), 2.82 (s, 6H), 1.18 (t, J = 7.1, 3H); rotational isomer mixture.

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-pyrrolidin-1-ylethanone ("A13");
yield: 53 mg (46%); LC-MS retention time: 1.64 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.95 (dd, J = 8.6, 1.7, 1H), 7.92 (s, 1H), 7.74 (d, J = 8.6, 1H), 7.47 (d, J = 7.5, 1H), 7.34 (dt, J = 23.5, 7.3, 2H), 7.25 (d, J = 7.5, 1H), 5.06 (s, 2H), 4.79 (s, 2H), 3.83 (s, 2H), 3.51 (t, J = 6.8, 2H), 3.31 (t, J = 6.8, 2H), 1.93 – 1.86 (m, 2H), 1.78 (p, J = 6.9, 2H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-(2-methylpyrrolidin-1-yl)ethanone ("A14")



LC-MS retention time: 1.71 min;

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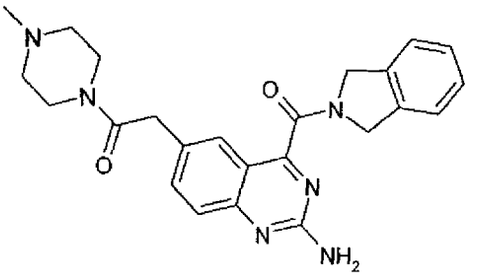
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.99 – 7.88 (m, 2H), 7.74 (dd, J = 8.6, 3.7, 1H), 7.48 (d, J = 7.5, 1H), 7.34 (dt, J = 23.5, 7.2, 2H), 7.25 (d, J = 7.5, 1H), 5.05 (s, 2H), 4.79 (s, 2H), 4.25 – 3.74 (m, 3H), 3.59 – 3.29 (m, 2H), 2.04 – 1.45 (m, 4H), 1.24 – 1.02 (m, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-(2,5-dimethylpyrrolidin-1-yl)ethanone ("A15");
LC-MS retention time: 1.81 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.96 (dd, J = 8.6, 1.8, 1H), 7.92 (d, J = 1.3, 1H), 7.75 (d, J = 8.6, 1H), 7.47 (d, J = 7.5, 1H), 7.34 (dt, J = 23.5, 7.2, 2H), 7.25 (d, J = 7.5, 1H), 5.06 (s, 2H), 4.80 (s, 2H), 4.22 – 4.11 (m, 1H), 3.99 – 3.88 (m, 2H), 3.82 – 3.76 (m, 1H), 2.07 – 1.87 (m, 2H), 1.67 – 1.57 (m, 2H), 1.24 – 1.17 (m, 6H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-methylacetamide ("A16");
LC-MS retention time: 1.39 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.99 (dd, J = 8.7, 1.7, 1H), 7.94 (s, 1H), 7.74 (d, J = 8.6, 1H), 7.48 (d, J = 7.5, 1H), 7.34 (dt, J = 23.1, 7.2, 2H), 7.25 (d, J = 7.3, 1H), 5.06 (s, 2H), 4.81 (s, 2H), 3.60 (s, 2H), 2.58 (s, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-(4-methylpiperazin-1-yl)ethanone ("A17")



LC-MS retention time: 1.16 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.91 (dd, J = 8.6, 1.8, 1H), 7.88 (s, 1H), 7.75 (d, J = 8.6, 1H), 7.48 (d, J = 7.3, 1H), 7.34 (dt, J = 22.7, 7.4,

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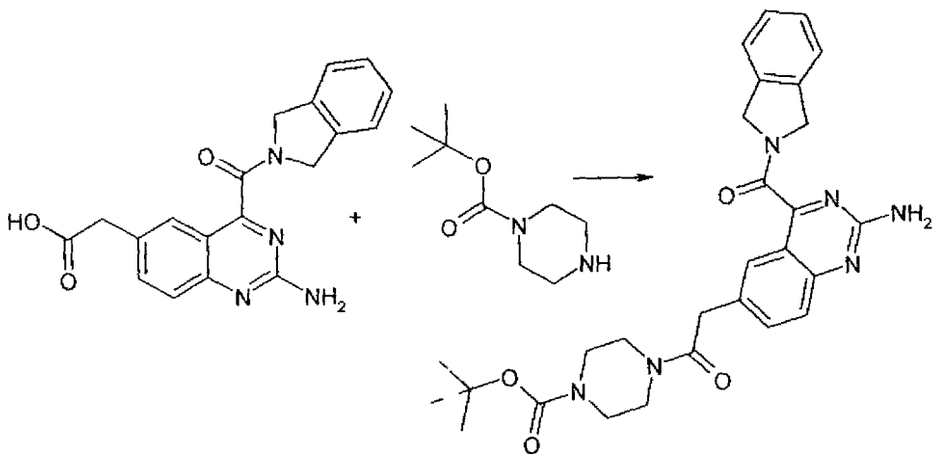
2H), 7.26 (d, J = 7.5, 1H), 5.05 (s, 2H), 4.82 (s, 2H), 4.05 – 3.91 (m, 2H), 3.59 – 3.33 (m, 4H), 3.17 – 2.90 (m, 4H), 2.85 (s, 3H).

Example 6

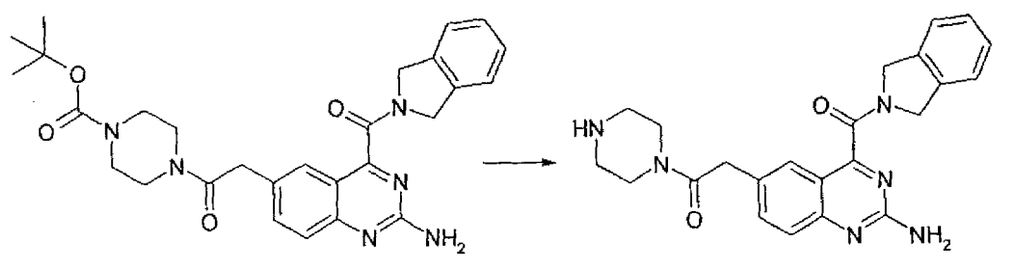
Preparation of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-piperazin-1-ylethanone ("A18")

Step 1: 4-[2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetyl]-piperazine-1-tert-butylcarboxylate



The compound is obtained in accordance with the preceding process (Example 5). LC-MS retention time: 1.88 min.

Step 2: 2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-1-piperazin-1-ylethanone



4-[2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetyl]piperazine-1-tert-butylcarboxylate is dissolved in 5 ml of dichloromethane/trifluoroacetic acid (1:1) and stirred at 23°C for 60 min. The mixture is subsequently evaporated to

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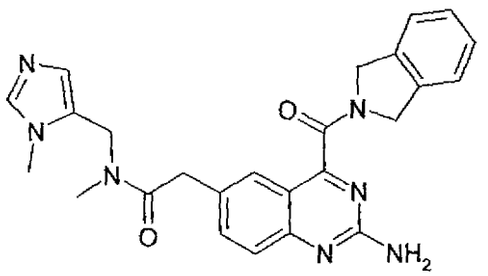
dryness in vacuo, taken up in 1 ml of DMSO and purified preparatively on the reversed phase. Yield: 100 mg (84%); LC-MS retention time: 1.16 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.91 (dd, J = 8.6, 1.8, 1H), 7.88 (s, 1H), 7.76 (d, J = 8.6, 1H), 7.48 (d, J = 7.5, 1H), 7.34 (dt, J = 22.6, 7.2, 2H), 7.26 (d, J = 7.3, 1H), 5.05 (s, 2H), 4.81 (s, 2H), 3.97 (s, 2H), 3.73 (d, J = 42.5, 4H), 3.15 (d, J = 37.0, 4H).

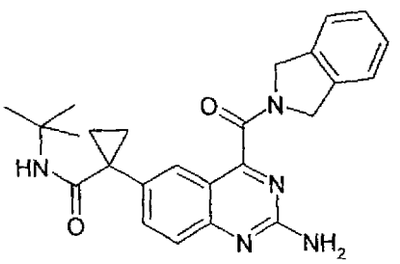
The following compounds are obtained analogously to Example 5:

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-methyl-N-[(3-methyl-imidazol-4-yl)methyl]acetamide ("A19")



LC-MS retention time: 1.22 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 9.06 (s, 1H), 7.94 (dt, J = 7.9, 4.0, 1H), 7.92 (s, 1H), 7.75 (d, J = 8.6, 1H), 7.66 (s, 1H), 7.48 (d, J = 7.5, 1H), 7.34 (dt, J = 23.3, 7.3, 2H), 7.25 (d, J = 7.5, 1H), 5.05 (s, 2H), 4.81 (s, 2H), 4.65 (s, 2H), 3.97 (d, J = 17.8, 2H), 3.77 (s, 3H), 3.07 (s, 3H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-tert-butylcyclo-propanecarboxamide ("A20")



LC-MS retention time: 1.92 min;

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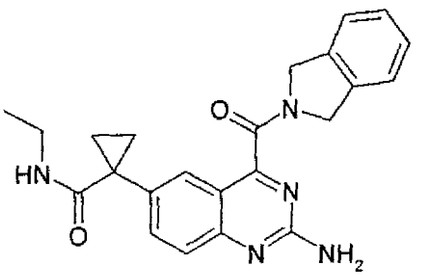
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.11 (s, 1H), 8.02 – 7.97 (m, 1H), 7.77 (d, J = 9.4, 1H), 7.46 (d, J = 7.5, 1H), 7.34 (dt, J = 14.9, 7.2, 2H), 7.24 (d, J = 7.3, 1H), 5.08 (s, 2H), 4.84 (s, 2H), 1.42 – 1.38 (m, 2H), 1.16 (s, 9H), 1.06 (dd, J = 6.9, 4.3, 2H).

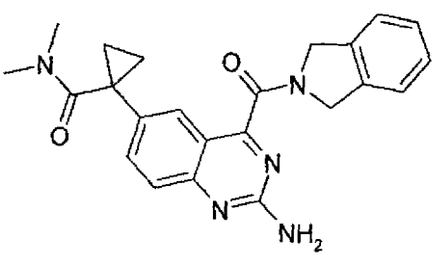
1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethylcyclopropanecarboxamide ("A21")



LC-MS retention time: 1.66 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.99 (dd, J = 8.6, 1.9, 1H), 7.92 (d, J = 1.7, 1H), 7.73 (d, J = 8.9, 1H), 7.45 (d, J = 7.3, 1H), 7.36 – 7.26 (m, 2H), 7.22 (d, J = 7.3, 1H), 5.03 (s, 2H), 4.78 (s, 2H), 2.97 (q, J = 7.1, 3H), 1.40 – 1.35 (m, 2H), 1.02 (dd, J = 6.6, 4.0, 2H), 0.85 (t, J = 7.2, 3H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N,N-dimethylcyclopropanecarboxamide ("A22")



LC-MS retention time: 1.50 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.76 (dd, J = 8.9, 2.0, 1H), 7.70 (d, J = 8.7, 1H), 7.63 (d, J = 1.7, 1H), 7.41 (d, J = 7.3, 1H), 7.33 – 7.23 (m, 2H), 7.19 (d, J = 5.5, 1H), 5.00 (s, 2H), 4.78 (s, 2H), 2.73 (s, 6H), 1.35 – 1.32 (m, 1H), 1.23 – 1.20 (m, 1H).

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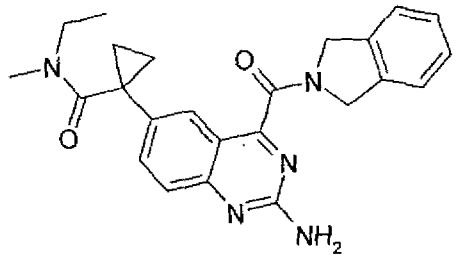
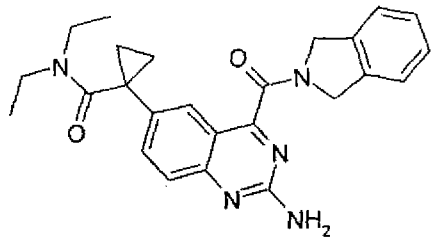
1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-N-methylcyclopropanecarboxamide ("A23")



LC-MS retention time: 1.69 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.81 – 7.60 (m, 3H), 7.40 (d, J = 7.2, 1H), 7.33 – 7.22 (m, 2H), 7.18 (d, J = 7.3, 1H), 4.98 (s, 2H), 4.77 (s, 2H), 3.22 (q, J = 7.1, 2H), 2.69 (s, 3H), 1.35 – 1.31 (m, 2H), 1.26 – 1.18 (m, 2H), 0.95 – 0.84 (m, 3H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N,N-diethylcyclopropanecarboxamide ("A24")



LC-MS retention time: 1.79 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.78 (dd, J = 8.9, 2.0, 1H), 7.72 (d, J = 8.9, 1H), 7.65 (d, J = 1.8, 1H), 7.46 (d, J = 7.2, 1H), 7.37 – 7.28 (m, 2H), 7.23 (d, J = 7.0, 1H), 4.98 (s, 2H), 4.78 (s, 2H), 3.21 (q, J = 7.0, 4H), 1.36 (dd, J = 6.8, 4.9, 2H), 1.24 (dd, J = 6.9, 5.0, 2H), 1.00 – 0.92 (m, 3H), 0.78 – 0.70 (m, 3H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-hydroxyethyl)-N-methylcyclopropanecarboxamide ("A25")

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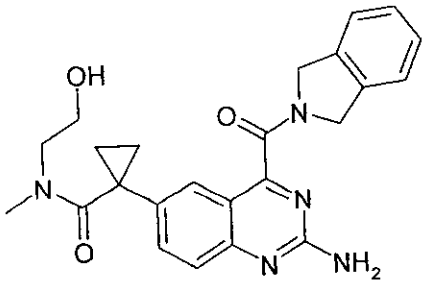
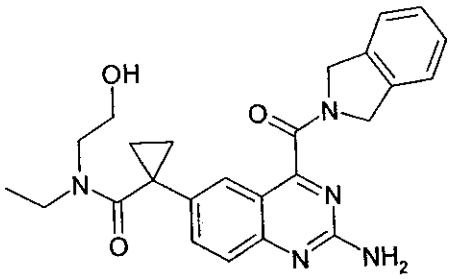


LC-MS retention time: 1.48 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.76 (d, J = 8.8, 1H), 7.70 (d, J = 8.8, 2H), 7.40 (d, J = 7.5, 1H), 7.27 (dt, J = 22.2, 7.1, 2H), 7.19 (d, J = 7.5, 1H), 5.00 (s, 2H), 4.79 (s, 2H), 3.53 – 3.44 (m, 2H), 3.35 – 3.25 (m, 2H), 2.79 (s, 3H), 1.43 – 1.37 (m, 2H), 1.26 – 1.19 (m, 2H); rotational isomer mixture.

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-hydroxyethyl)-N-ethylcyclopropanecarboxamide ("A26")



LC-MS retention time: 1.54 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.74 – 7.61 (m, 3H), 7.34 (d, J = 7.3, 1H), 7.22 (dt, J = 22.2, 7.5, 2H), 7.12 (d, J = 7.3, 1H), 4.97 (s, 2H), 4.74 (s, 2H), 3.36 – 3.09 (m, 4H), 1.41 – 1.29 (m, 3H), 1.19 – 1.15 (m, 2H), 0.95 – 0.86 (m, 2H), 0.76 – 0.64 (m, 2H).

[2-Amino-6-[1-(pyrrolidine-1-carbonyl)cyclopropyl]quinazolin-4-yl]isoindolin-2-ylmethanone ("A27")

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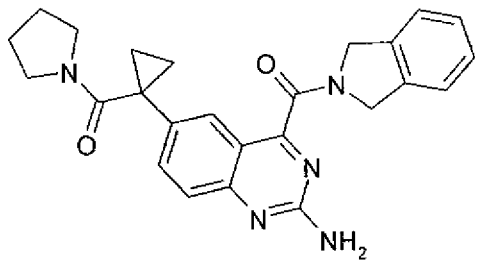
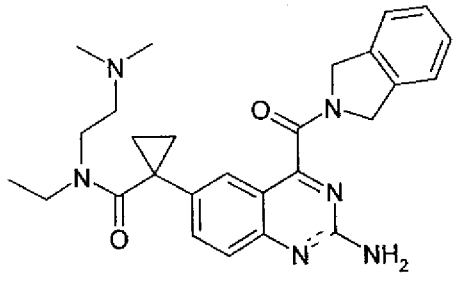


LC-MS retention time: 1.68 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.71 – 7.67 (m, 1H), 7.65 (d, J = 8.8, 1H), 7.62 (d, J = 1.8, 1H), 7.35 (d, J = 7.3, 1H), 7.27 – 7.16 (m, 2H), 7.12 (d, J = 7.3, 1H), 4.96 (s, 2H), 4.72 (s, 2H), 3.24 – 3.00 (m, 4H), 1.55 – 1.49 (m, 4H), 1.37 – 1.30 (m, 2H), 1.14 – 1.10 (m, 2H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-dimethylamino-ethyl)-N-ethylcyclopropanecarboxamide ("A28")



LC-MS retention time: 1.31 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.99 – 7.91 (m, 2H), 7.76 (d, J = 8.6, 1H), 7.47 (d, J = 7.5, 1H), 7.34 (dt, J = 23.5, 7.2, 2H), 7.25 (d, J = 7.5, 1H), 5.07 (s, 2H), 4.81 (s, 2H), 3.96 (s, 2H), 3.63 (t, J = 6.4, 2H), 3.48 (q, J = 7.0, 2H), 3.25 (t, J = 6.5, 2H), 2.82 (s, 6H), 1.52 (dd, J = 7.0, 4.0, 2H), 1.20 (dd, J = 7.0, 4.0, 2H), 1.18 (t, J = 7.1, 3H); rotational isomer mixture.

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-tert-butylcyclobutane-carboxamide ("A29")

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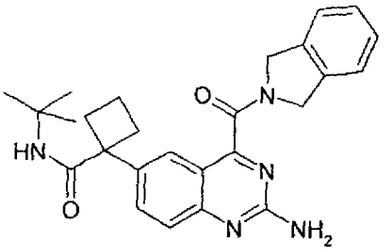
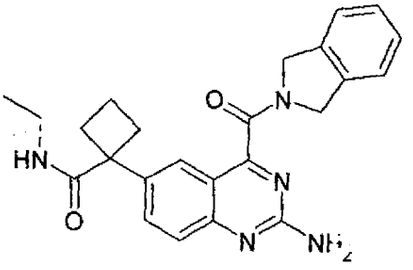


(Preparation by reaction of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclobutanecarboxylic acid ["A61"] with tert-butylamine)
LC-MS retention time: 1.99 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.12 (dd, J = 8.9, 2.0, 1H), 7.98 (d, J = 1.8, 1H), 7.79 (d, J = 8.9, 1H), 7.47 (d, J = 7.3, 1H), 7.34 (dt, J = 19.7, 7.1, 2H), 7.23 (d, J = 7.6, 1H), 5.09 (s, 2H), 4.80 (s, 2H), 2.79 – 2.68 (m, 2H), 2.44 – 2.32 (m, 2H), 1.94 – 1.72 (m, 2H), 1.14 (s, 9H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N-ethylcyclobutane-carboxamide ("A30")



LC-MS retention time: 1.73 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.03 (dd, J = 8.7, 1.9, 1H), 7.91 (d, J = 1.8, 1H), 7.76 (d, J = 8.8, 1H), 7.48 (d, J = 7.5, 1H), 7.34 (dt, J = 22.9, 7.2, 2H), 7.25 (d, J = 7.3, 1H), 5.07 (s, 2H), 4.81 (s, 2H), 2.99 (q, J = 7.2, 2H), 2.78 – 2.70 (m, 2H), 2.43 – 2.34 (m, 2H), 1.89 – 1.70 (m, 2H), 0.87 (t, J = 7.2, 3H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N-methylcyclobutane-carboxamide ("A31")

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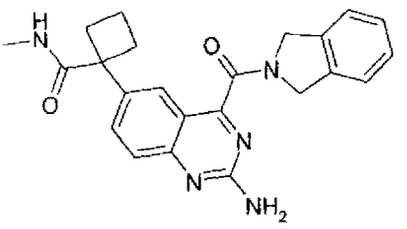
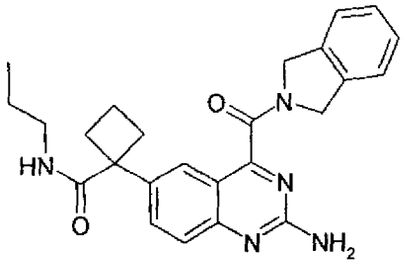


LC-MS retention time: 1.66 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.00 (dd, J = 8.7, 1.9, 1H), 7.91 (d, J = 1.8, 1H), 7.75 (d, J = 8.8, 1H), 7.48 (d, J = 7.5, 1H), 7.35 (dt, J = 22.0, 7.3, 2H), 7.27 (d, J = 7.3, 1H), 5.07 (s, 2H), 4.84 (s, 2H), 2.77 – 2.68 (m, 2H), 2.49 (d, J = 6.2, 3H), 2.43 – 2.33 (m, 2H), 1.91 – 1.68 (m, 2H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N-propylcyclobutane-carboxamide ("A32")

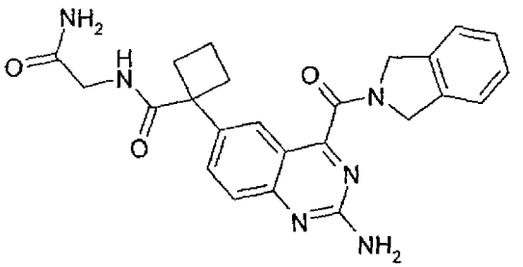


LC-MS retention time: 1.63 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.04 (dd, J = 8.8, 2.0, 1H), 7.91 (d, J = 1.8, 1H), 7.76 (d, J = 8.8, 1H), 7.48 (d, J = 7.3, 1H), 7.34 (dt, J = 23.1, 7.2, 2H), 7.25 (d, J = 7.5, 1H), 5.07 (s, 2H), 4.80 (s, 2H), 2.92 (t, J = 7.1, 2H), 2.78 – 2.71 (m, 2H), 2.43 – 2.35 (m, 2H), 1.89 – 1.70 (m, 2H), 1.31 – 1.22 (m, 2H), 0.65 (t, J = 7.3, 3H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-amino-2-oxoethyl)-cyclobutanecarboxamide ("A33")

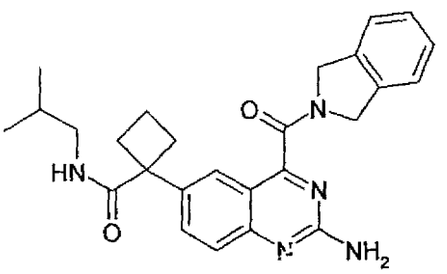
Aquaforest TIFF Junction Evaluation



LC-MS retention time: 1.05 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.04 (dd, J = 8.8, 2.0, 1H), 7.97 (d, J = 1.8, 1H), 7.75 (d, J = 8.8, 1H), 7.48 (d, J = 7.3, 1H), 7.34 (dt, J = 21.5, 7.2, 2H), 7.26 (d, J = 7.3, 1H), 5.07 (s, 2H), 4.83 (s, 2H), 3.54 (s, 2H), 2.84 – 2.76 (m, 2H), 2.44 – 2.36 (m, 2H), 1.95 – 1.70 (m, 2H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N-isobutylcyclobutane-carboxamide ("A34")



LC-MS retention time: 1.93 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.04 (dd, J = 8.7, 1.9, 1H), 7.93 (d, J = 1.8, 1H), 7.76 (d, J = 8.6, 1H), 7.48 (d, J = 7.7, 1H), 7.34 (dt, J = 23.7, 7.4, 2H), 7.24 (d, J = 7.5, 1H), 5.07 (s, 2H), 4.79 (s, 2H), 2.83 – 2.70 (m, 4H), 2.43 – 2.35 (m, 2H), 1.91 – 1.69 (m, 2H), 1.60 – 1.51 (m, 1H), 0.64 (d, J = 6.8, 6H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-tert-butyl-2-methyl-propanamide ("A35")

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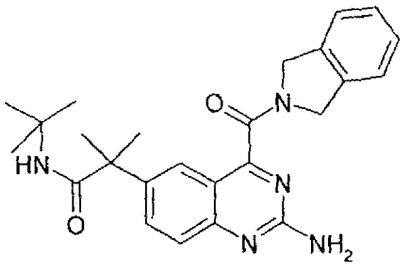
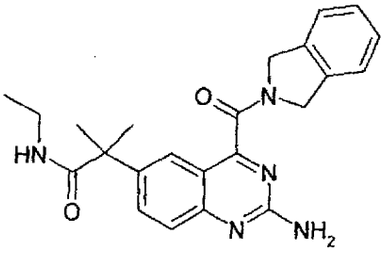


(Preparation by reaction of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylpropanoic acid ["A62"] with tert-butylamine);
LC-MS retention time: 1.54 min ("nonpolar" gradient);
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.04 (dd, J = 8.9, 2.1, 1H), 7.87 (d, J = 2.0, 1H), 7.78 (d, J = 8.9, 1H), 7.46 (d, J = 7.3, 1H), 7.34 (dt, J = 18.0, 7.2, 2H), 7.25 (d, J = 7.2, 1H), 5.06 (s, 2H), 4.84 (s, 2H), 1.50 (s, 6H), 1.19 (s, 9H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-2-methyl-propanamide ("A36")



LC-MS retention time: 1.19 min ("nonpolar" gradient);
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.02 (dd, J = 8.9, 2.1, 1H), 7.85 (d, J = 2.0, 1H), 7.75 (d, J = 8.9, 1H), 7.48 (d, J = 7.2, 1H), 7.40 – 7.29 (m, 2H), 7.26 (d, J = 7.3, 1H), 5.05 (s, 2H), 4.82 (s, 2H), 3.02 (q, J = 7.2, 2H), 1.49 (s, 6H), 0.90 (t, J = 7.2, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-isobutyl-2-methyl-propanamide ("A37")

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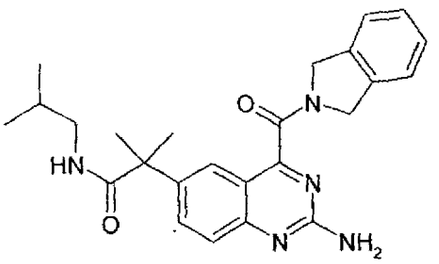
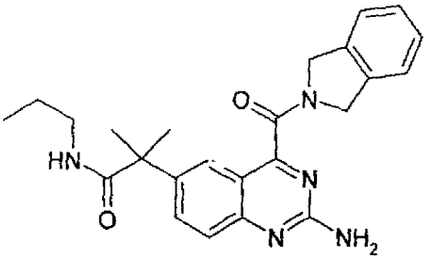


LC-MS retention time: 1.47 min ("nonpolar" gradient);
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.02 (dd, J = 8.9, 2.1, 1H), 7.85 (d, J = 2.0, 1H), 7.75 (d, J = 8.9, 1H), 7.48 (d, J = 7.2, 1H), 7.40 – 7.29 (m, 2H), 7.26 (d, J = 7.3, 1H), 5.05 (s, 2H), 4.82 (s, 2H), 3.02 (q, J = 7.2, 2H), 1.49 (s, 6H), 0.90 (t, J = 7.2, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-propyl-2-methyl-propanamide ("A38")



LC-MS retention time: 1.33 min ("nonpolar" gradient);
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.02 (dd, J = 8.9, 2.1, 1H), 7.85 (d, J = 2.0, 1H), 7.75 (d, J = 8.8, 1H), 7.48 (d, J = 7.5, 1H), 7.34 (dt, J = 21.5, 7.2, 2H), 7.26 (d, J = 7.3, 1H), 5.05 (s, 2H), 4.81 (s, 2H), 2.95 (t, J = 7.1, 2H), 1.50 (s, 6H), 1.38 – 1.27 (m, 2H), 0.69 (t, J = 7.4, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-(2-amino-2-oxoethyl)-2-methylpropanamide ("A39")

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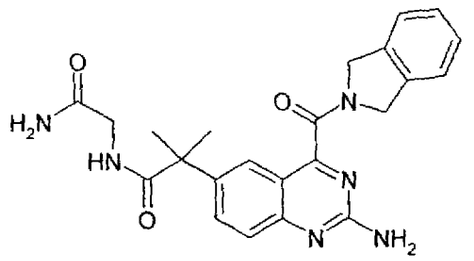
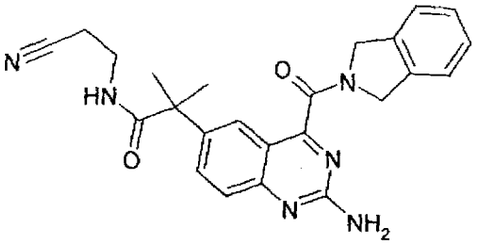


LC-MS retention time: 1.48 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.09 (dd, J = 9.0, 2.0, 1H), 7.97 (d, J = 2.0, 1H), 7.74 (d, J = 8.8, 1H), 7.48 (d, J = 7.3, 1H), 7.34 (dt, J = 21.8, 7.1, 2H), 7.26 (d, J = 7.3, 1H), 5.07 (s, 2H), 4.84 (s, 2H), 3.59 (s, 2H), 1.54 (s, 6H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]- N-(2-cyanoethyl)-2-methylpropanamide ("A40")



LC-MS retention time: 1.64 min:

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.02 (dd, J = 8.9, 2.1, 1H), 7.91 (d, J = 2.0, 1H), 7.74 (d, J = 9.0, 1H), 7.48 (d, J = 7.3, 1H), 7.34 (dt, J = 21.1, 7.4, 2H), 7.26 (d, J = 7.5, 1H), 5.06 (s, 2H), 4.85 (s, 2H), 3.25 (t, J = 6.5, 2H), 2.59 (t, J = 6.5, 2H), 1.52 (s, 6H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-methyl-5,5-difluoro-pentanamide ("A41")

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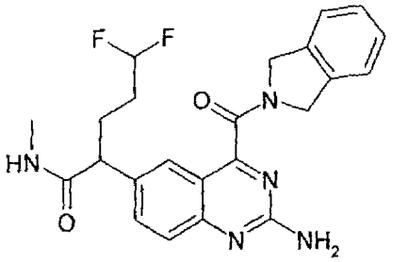
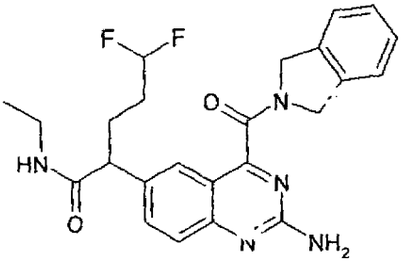


(Preparation by reaction of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5,5-difluoropentanoic acid ["A63"] with methylamine);

LC-MS retention time: 1.26 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.08 – 8.03 (m, 1H), 7.93 (d, J = 1.7, 1H), 7.72 (d, J = 8.8, 1H), 7.43 (d, J = 7.5, 1H), 7.30 (dt, J = 22.6, 7.1, 2H), 7.21 (d, J = 7.5, 1H), 5.95 (tt, J = 56.9, 4.0, 1H), 5.03 (s, 2H), 4.79 (s, 2H), 3.63 (dd, J = 8.9, 5.8, 1H), 2.08 (dd, J = 19.1, 8.4, 1H), 1.81 – 1.53 (m, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-5,5-difluoro-pentanamide ("A42")



LC-MS retention time: 1.76 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.06 (t, J = 5.4, 1H), 7.75 (dd, J = 8.9, 1.9, 1H), 7.63 (d, J = 1.8, 1H), 7.49 (d, J = 9.0, 1H), 7.38 – 7.27 (m, 2H), 7.26 (d, J = 7.7, 1H), 7.01 (s, 2H), 6.18 – 5.89 (m, 1H), 5.00 (s, 2H), 4.67 (s, 2H), 3.51 (dd, J = 8.9, 5.4, 1H), 3.10 – 2.89 (m, 2H), 2.14 – 1.53 (m, 4H), 0.90 (t, J = 7.2, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethylpentanamide ("A43")

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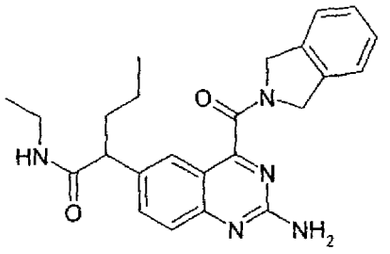
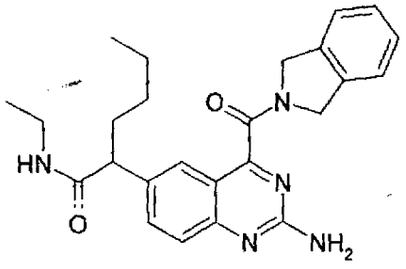


(Preparation by reaction of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]pentanoic acid ["A64"] with ethylamine);

LC-MS retention time: 1.77 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.03 (t, J = 5.5, 1H), 7.76 (dd, J = 8.9, 1.9, 1H), 7.59 (d, J = 1.8, 1H), 7.46 (d, J = 8.9, 1H), 7.35 – 7.24 (m, 3H), 7.00 (s, 2H), 4.99 (s, 2H), 4.66 (s, 2H), 3.46 (dd, J = 9.5, 5.8, 1H), 3.08 – 2.87 (m, 2H), 1.98 – 1.46 (m, 2H), 1.26 – 1.07 (m, 2H), 0.89 (t, J = 7.2, 3H), 0.83 (t, J = 7.3, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethylhexanamide ("A44")



(Preparation by reaction of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]hexanoic acid ["A65"] with ethylamine)

LC-MS retention time: 1.89 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.07 (dd, J = 8.6, 1.8, 1H), 7.89 (d, J = 1.7, 1H), 7.71 (d, J = 8.8, 1H), 7.46 (d, J = 7.5, 1H), 7.31 (dt, J = 23.9, 7.3, 2H), 7.22 (d, J = 7.5, 1H), 5.03 (s, 2H), 4.78 (s, 2H), 3.55 (dd, J = 8.7, 6.5, 1H), 3.07 – 2.85 (m, 2H), 2.00 – 1.50 (m, 2H), 1.28 – 1.19 (m, 2H), 1.19 – 1.04 (m, 2H), 0.89 (t, J = 7.2, 3H), 0.78 (t, J = 7.2, 3H).

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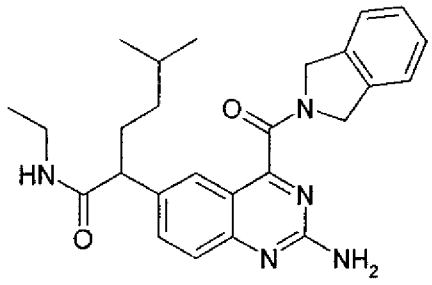
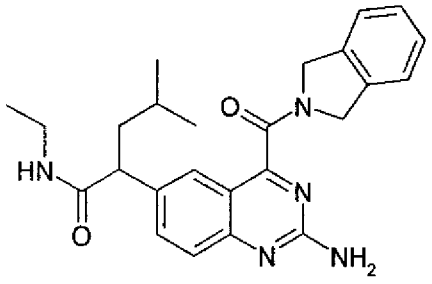
2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-5-methyl-hexanamide ("A45")



(Preparation by reaction of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5-methylhexanoic acid ["A70"] with ethylamine);
LC-MS retention time: 2.04 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.11 (dd, J = 8.8, 1.8, 1H), 7.92 (d, J = 1.7, 1H), 7.75 (d, J = 8.8, 1H), 7.49 (d, J = 7.5, 1H), 7.34 (dt, J = 24.2, 7.2, 2H), 7.25 (d, J = 7.5, 1H), 5.07 (s, 2H), 4.81 (s, 2H), 3.55 (dd, J = 8.4, 6.8, 1H), 3.10 – 2.92 (m, 2H), 2.03 – 1.89 (m, 1H), 1.69 – 1.57 (m, 1H), 1.55 – 1.43 (m, 1H), 1.16 – 0.96 (m, 2H), 0.93 (t, J = 7.2, 3H), 0.80 (dd, J = 6.7, 2.3, 6H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-4-methyl-pentanamide ("A46")



(Preparation by reaction of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]4-methylpentanoic acid ["A71"] with ethylamine);
LC-MS retention time: 1.92 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.07 (dd, J = 8.8, 1.8, 1H), 7.90 (d, J = 1.8, 1H), 7.71 (d, J = 8.6, 1H), 7.45 (d, J = 7.5, 1H), 7.31 (dt, J =

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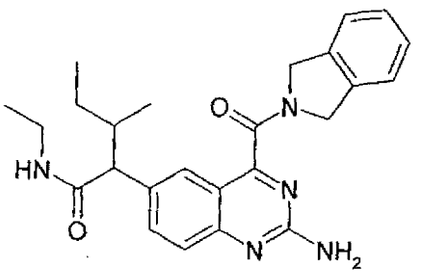
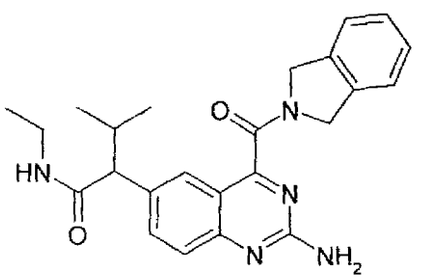
23.5, 7.2, 2H), 7.21 (d, J = 7.5, 1H), 5.04 (s, 2H), 4.78 (s, 2H), 3.69 (dd, J = 8.8, 6.6, 1H), 3.02 (dq, J = 14.5, 7.2, 1H), 2.91 (dq, J = 14.3, 7.2, 1H), 1.88 (ddd, J = 13.2, 8.8, 6.4, 1H), 1.46 (dt, J = 13.4, 6.9, 1H), 1.36 (td, J = 13.2, 6.6, 1H), 0.88 (t, J = 7.2, 3H), 0.82 (dd, J = 14.0, 6.6, 6H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-3-methyl-pentanamide ("A47")



(Preparation by reaction of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-3-methylpentanoic acid ["A72"] with ethylamine);
LC-MS retention time: 1.24 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.14 – 8.09 (m, 1H), 7.91 (d, J = 1.5, 1H), 7.75 (d, J = 8.8, 1H), 7.49 (d, J = 7.5, 1H), 7.35 (dt, J = 24.6, 7.3, 2H), 7.25 (d, J = 7.5, 1H), 5.06 (s, 2H), 4.81 (s, 2H), 3.29 (dd, J = 10.8, 6.2, 1H), 3.06 (ddd, J = 14.5, 9.6, 6.1, 1H), 2.90 (dq, J = 14.5, 7.2, 1H), 2.18 – 2.04 (m, 1H), 1.49 (ddd, J = 13.4, 7.7, 3.3, 1H), 1.20 – 1.02 (m, 1H), 0.96 – 0.82 (m, 6H), 0.69 (t, J = 7.4, 1H), 0.58 (d, J = 6.8, 2H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-3-methyl-butan-amide ("A48")



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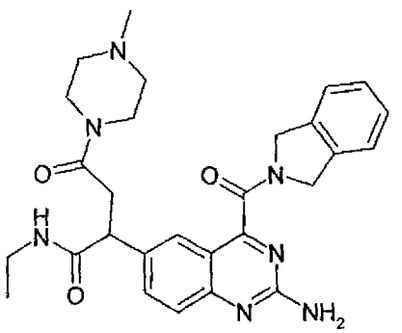
(Preparation by reaction of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-3-methylbutanoic acid ["A73"] with ethylamine);
LC-MS retention time: 1.80 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.07 (dd, J = 8.8, 1.8, 1H), 7.89 (d, J = 1.7, 1H), 7.70 (d, J = 8.7, 1H), 7.42 (d, J = 7.5, 1H), 7.28 (dt, J = 20.1, 7.4, 2H), 7.18 (d, J = 7.5, 1H), 5.02 (s, 2H), 4.77 (s, 2H), 3.13 (d, J = 10.7, 1H), 3.09 – 2.80 (m, 2H), 2.31 – 2.16 (m, 1H), 0.95 – 0.85 (m, 6H), 0.62 – 0.51 (m, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-4-(4-methylpiperazin-1-yl)-4-oxobutanamide ("A49")



(Preparation by reaction of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-(4-methylpiperazin-1-yl)-4-oxobutanoic acid ["A75"] with ethylamine);
LC-MS retention time: 1.24 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.09 (d, J = 8.8, 1H), 8.00 (s, 1H), 7.76 (d, J = 8.8, 1H), 7.49 (d, J = 7.5, 1H), 7.38 (t, J = 7.4, 1H), 7.33 (t, J = 7.4, 1H), 7.26 (s, 1H), 5.10 (s, 2H), 4.81 (s, 2H), 4.42 (s, 1H), 4.18 (s, 2H), 3.52 – 2.62 (m, 13H), 0.89 (t, J = 7.2, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N'-ethyl-2-methylene-pentanediamide ("A50")

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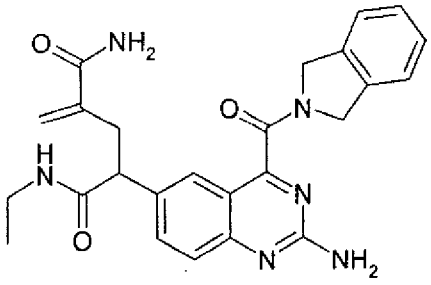
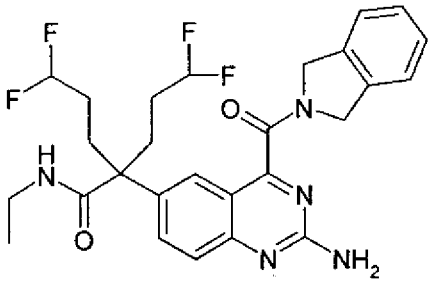


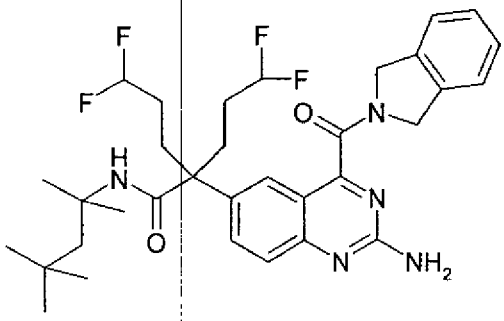
(Preparation by reaction of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-carbamoylpent-4-enoic acid ["A74"] with ethylamine);
LC-MS retention time: 1.66 min.

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-N-ethyl-5,5-difluoropentanamide ("A51")



(Preparation by reaction of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-5,5-difluoropentanoic acid ["A66"] with ethylamine);
LC-MS retention time: 1.99 min.

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-5,5-difluoro-N-(1,1,3,3-tetramethylbutyl)pentanamide ("A52")



LC-MS retention time: 2.25 min ("nonpolar" gradient).

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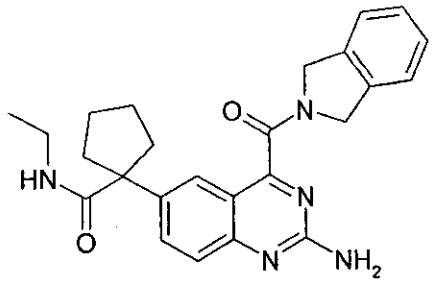
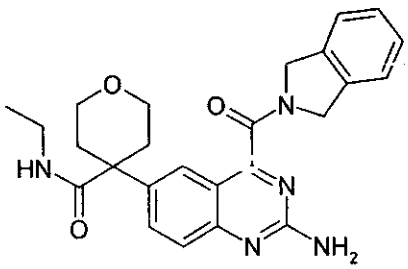
1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethylcyclopentane-carboxamide ("A53")



(Preparation by reaction of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclopentanecarboxylic acid ["A68"] with ethylamine);
LC-MS retention time: 1.84 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.74 (dd, J = 9.1, 2.1, 1H), 7.70 (t, J = 5.6, 1H), 7.61 (d, J = 2.0, 1H), 7.45 (d, J = 7.5, 1H), 7.33 (t, J = 7.4, 1H), 7.28 (t, J = 7.2, 1H), 7.25 (d, J = 7.3, 1H), 4.99 (s, 2H), 4.66 (s, 2H), 3.74 (d, J = 11.7, 2H), 3.46 – 3.38 (m, 2H), 3.03 – 2.95 (m, 2H), 2.42 – 2.34 (m, 2H), 1.85 – 1.75 (m, 2H), 0.86 (t, J = 7.2, 3H).

1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyltetrahydropyran-4-carboxamide ("A54")



(Preparation by reaction of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]tetrahydropyran-4-carboxylic acid ["A69"] with ethylamine);
LC-MS retention time: 1.59 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.74 (dd, J = 9.1, 2.1, 1H), 7.70 (t, J = 5.6, 1H), 7.61 (d, J = 2.0, 1H), 7.45 (d, J = 7.5, 1H), 7.33 (t, J = 7.4, 1H), 7.28 (t, J = 7.2, 1H), 7.25 (d, J = 7.3, 1H), 4.99 (s, 2H), 4.66 (s, 2H), 3.74

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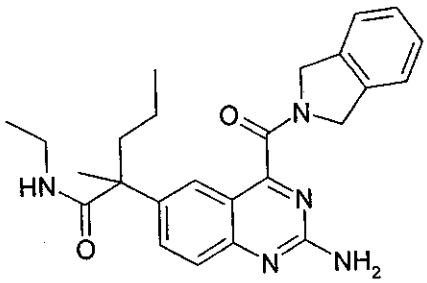
(d, J = 11.7, 2H), 3.46 – 3.38 (m, 2H), 3.03 – 2.95 (m, 2H), 2.42 – 2.34 (m, 2H), 1.85 – 1.75 (m, 2H), 0.86 (t, J = 7.2, 3H).

2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-N-ethyl-2-methyl-pentanamide ("A55")



(Preparation by reaction of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl-2-methylpentanoic acid ["A67"] with ethylamine);

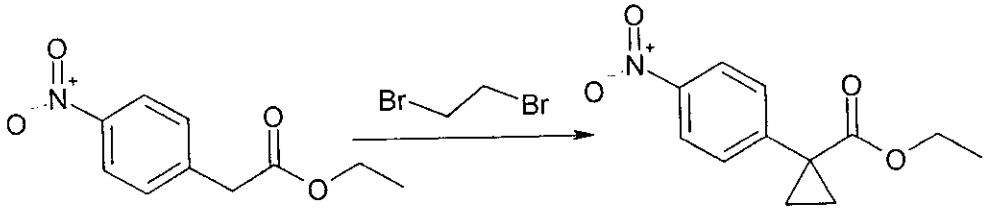
LC-MS retention time: 1.48 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.90 (dd, J = 9.0, 2.0, 1H), 7.76 (d, J = 1.8, 1H), 7.65 (d, J = 8.8, 1H), 7.35 (d, J = 7.5, 1H), 7.22 (dt, J = 22.4, 7.2, 2H), 7.13 (d, J = 7.3, 1H), 4.96 (s, 2H), 4.73 (s, 2H), 3.02 – 2.87 (m, 2H), 1.87 (td, J = 13.1, 4.7, 1H), 1.78 – 1.68 (m, 1H), 1.37 (s, 3H), 1.13 – 0.95 (m, 2H), 0.81 (t, J = 7.2, 3H), 0.75 (t, J = 7.2, 3H).

Example 7

Preparation of ethyl 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-cyclopropanecarboxylate ("A56") and 1-[2-amino-4-(isoindoline-2-carbonyl)-quinazolin-6-yl]cyclopropanecarboxylic acid ("A57")

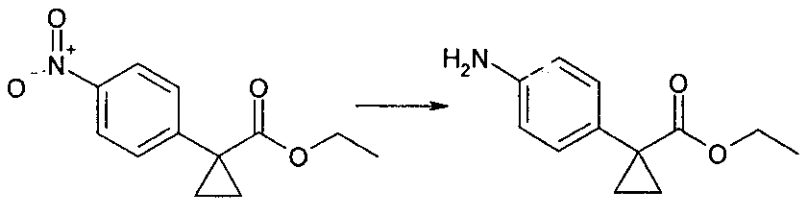
Step 1: Ethyl 1-(4-nitrophenyl)cyclopropanecarboxylate



20 g of ethyl 4-nitrophenylacetate are dissolved in in 30 ml of DMF and added dropwise to a suspension of 4 g of sodium hydride in 20 ml of DMF with ice-cooling. 8.5 ml of dibromoethane are subsequently added, and the mixture is stirred at 55°C for 1 h. A further 5 g of sodium hydride and 8.5 ml of dibromoethane are added with ice-cooling, and the mixture is then stirred at 50°C for 2 h. After cooling, the reaction mixture is stirred into a mixture of 100 ml of 1 N hydrochloric acid and 200 g of ice. The mixture is washed four times with 100 ml of diethyl ether each time, the combined organic phases once with 100 ml of sodium chloride solution, dried over sodium sulfate and, after filtration, evaporated to dryness in vacuo. The residue is purified by column chromatography (reversed phase). Yield: 8.5 g (38%) of ethyl 1-(4-nitrophenyl)cyclopropanecarboxylate; LC-MS retention time: 2.01 min ("nonpolar" gradient);

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.14 (d, J = 8.9, 2H), 7.60 (d, J = 8.9, 2H), 4.03 (q, J = 7.0, 2H), 1.56 (q, J = 4.1, 2H), 1.26 (q, J = 4.3, 2H), 1.08 (t, J = 7.0, 3H).

Step 2: Ethyl 1-(4-aminophenyl)cyclopropanecarboxylate



11.3 g of ethyl 1-(4-nitrophenyl)cyclopropanecarboxylate are dissolved in 110 ml of tetrahydrofuran, 1 g of 5% Pd/C (52.3% of water) is added, and the mixture is stirred at 23°C under a hydrogen atmosphere for 1 h. After aeration, the solid material is filtered off, and the filtrate is evaporated to dryness in vacuo. Yield: 9.8 g (100%) of ethyl 1-(4-aminophenyl)cyclopropanecarboxylate; LC-MS retention time: 1.18 min ("nonpolar" gradient).

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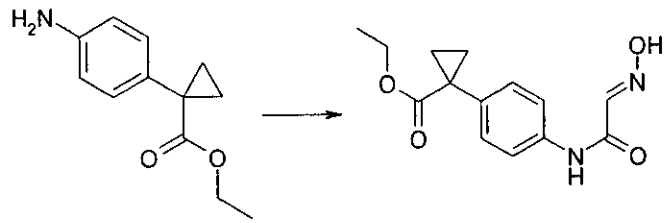
Step 3: Ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenylcyclopropanecarboxylate

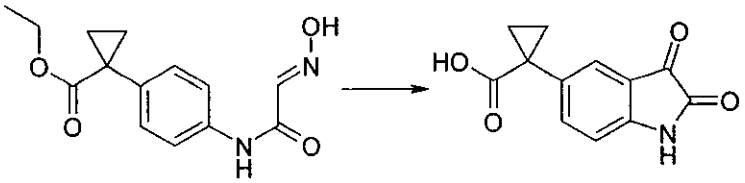


9 g of chloral hydrate are dissolved in 50 ml of water, 14 g of Na_2SO_4 are added, and the mixture is stirred at 23°C for 10 min. A solution of 10 g of ethyl 1-(4-aminophenyl)cyclopropanecarboxylate hydrochloride in 50 ml of water is added to this solution. 10 g of hydroxylammonium chloride in 20 ml of water are added to the resultant suspension, and the mixture is stirred at 60°C for 90 min. The mixture is subsequently allowed to cool, during which a precipitate deposits. This is filtered off, washed with water and dried at 40°C in vacuo. The mixture obtained is employed in the following reaction without further purification.

Yield: 12.5 g (95%) of ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]-phenylcyclopropanecarboxylate;

LC-MS retention time: 1.48 min.

Step 4: 1-(2,3-Dioxoindolin-5-yl))cyclopropanoic acid



12.5 g of ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenylcyclopropanecarboxylate are added in portions to 30 ml of sulfuric acid (98%) at 50°C, during which the temperature rises to 60°C. When the addition is

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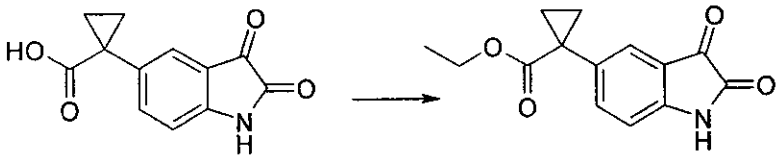
complete, the mixture is stirred for a further 30 min and subsequently poured into 400 ml of ice-water. The resultant precipitate is filtered off and washed with water. Drying at 40°C in vacuo gives 6.5 g (62%) of (2,3-dioxo-2,3-dihydro-1H-indol-5-yl)cyclopropanecarboxylic acid;
LC-MS retention time: 1.40 min.

Step 5: Ethyl 1-(2,3-dioxoindolin-5-yl)cyclopropanoate



6.5 g of (2,3-dioxo-2,3-dihydro-1H-indol-5-yl)cyclopropanecarboxylic acid are dissolved in 100 ml of ethanol, and 500 mg of toluene-4-sulfonic acid monohydrate are added. The mixture is heated at 80°C for 1 h and subsequently evaporated in vacuo. The residue is taken up in 100 ml of water and 100 ml of ethyl acetate and stirred at 60°C for a further 12 h. The mixture is neutralised using sodium hydrogencarbonate, and the organic phase is separated off. The aqueous phase is washed a further twice with 100 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate, filtered and evaporated to dryness in vacuo, giving 6.7 g (92%) of ethyl 1-(2,3-dioxoindolin-5-yl)cyclopropanecarboxylate; LC-MS retention time: 1.30 min.

Step 6: 5-(1-Ethoxycarbonylcyclopropyl)-1-tert-butoxycarbonyl-2,3-dioxo-indoline

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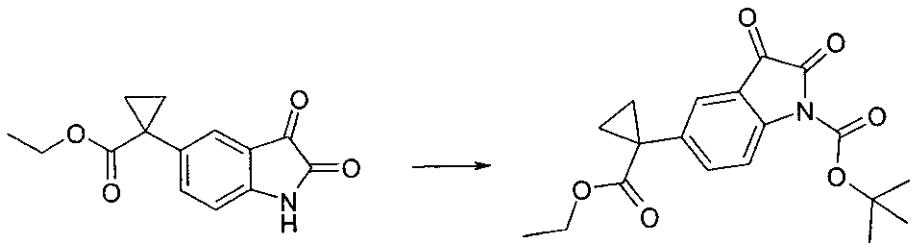
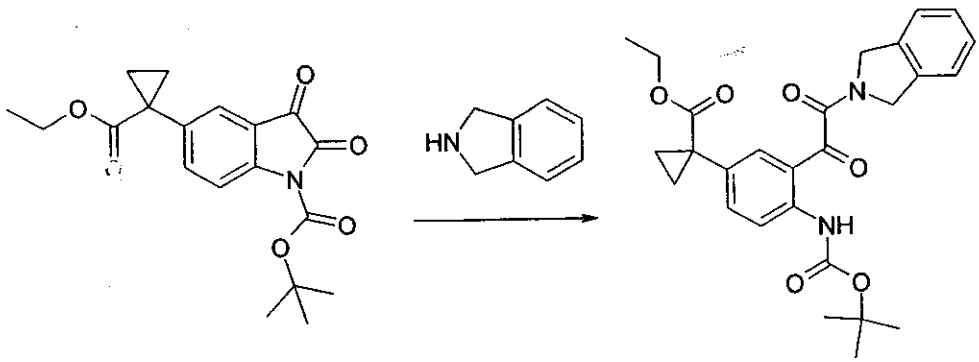


6 g of di-tert-butyl dicarbonate are added to 6.7 g of ethyl 1-(2,3-dioxo-indolin-5-yl))cyclopropanecarboxylate and 15 mg of 4-dimethylamino-pyridine in 100 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 12 h. The mixture is evaporated at 23°C in vacuo and processed further directly. Yield: 9.3 g (100%) of 5-(1-ethoxycarbonylcyclo-propyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline;
LC-MS retention time: 2.20 min ("nonpolar" gradient).

Step 7: Ethyl 1-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]cyclopropanecarboxylate



3.2 g of isoindoline are added to 9.3 g of 5-(1-ethoxycarbonylcyclopropyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline in 100 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 1 h. The mixture is evaporated to dryness in vacuo and purified by column chromatography, giving 4.0 g (32%) of ethyl 1-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]cyclopropanecarboxylate;
LC-MS retention time: 2.63 min ("nonpolar" gradient).

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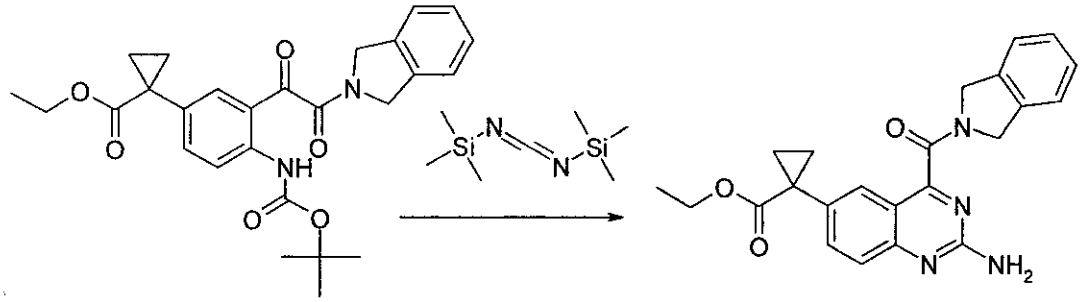
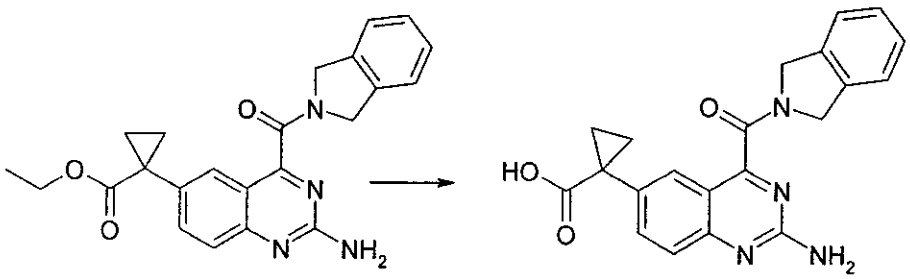
Step 8: Ethyl 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclopropanecarboxylate ("A56")



670 mg of ethyl 1-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]cyclopropanecarboxylate are dissolved in 15 ml of acetonitrile under argon. 213 mg of caesium fluoride and 380 µl of bis(trimethylsilyl)-carbodiimide are added to the solution. The mixture is stirred at room temperature for 15 min, and 2.7 ml of hydrochloric acid (1N) are then added, with the product precipitating as white solid. Yield: 510 mg (91%) of ethyl 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclopropanecarboxylate; LC-MS retention time: 1.65 min ("nonpolar" gradient); ^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.07 (dd, J = 8.7, 1.9, 1H), 8.00 (d, J = 1.8, 1H), 7.75 (d, J = 8.6, 1H), 7.46 (d, J = 7.3, 1H), 7.34 (dt, J = 22.6, 7.2, 2H), 7.25 (d, J = 7.3, 1H), 5.07 (s, 2H), 4.84 (s, 2H), 4.03 (q, J = 7.1, 2H), 1.59 (q, J = 4.0, 2H), 1.28 (q, J = 4.2, 2H), 1.08 (t, J = 7.1, 3H).

Step 9: 1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclopropanecarboxylic acid ("A57")



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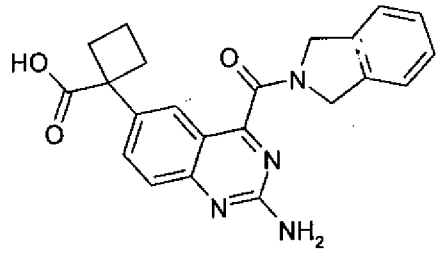
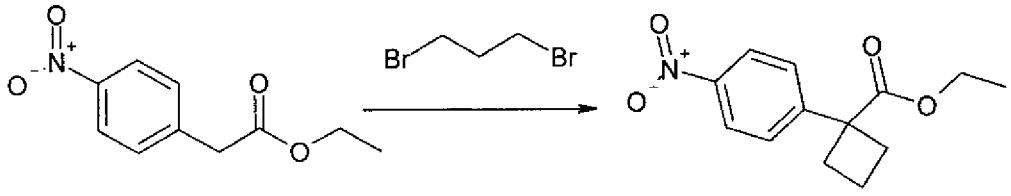
400 mg of ethyl 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclopropanecarboxylate are dissolved in 14 ml of tetrahydrofuran, and 3.5 ml of 2N sodium hydroxide solution are added. The mixture is stirred at 23°C for 12 h, evaporated to dryness in vacuo, taken up in 10 ml of water and adjusted to pH 2 using 1 ml of 25% hydrochloric acid. The resultant precipitate is filtered off and dried in vacuo. Yield: 250 mg (67%) of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclopropanecarboxylic acid;
LC-MS retention time: 1.63 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.05 (dd, J = 8.6, 1.8, 1H), 7.94 (d, J = 1.8, 1H), 7.70 (d, J = 8.6, 1H), 7.44 (d, J = 7.5, 1H), 7.31 (dt, J = 22.0, 7.2, 2H), 7.23 (d, J = 7.3, 1H), 5.03 (s, 2H), 4.80 (s, 2H), 1.52 (dd, J = 7.0, 4.0, 2H), 1.20 (dd, J = 7.0, 4.0, 2H).

Example 8

Preparation of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-cyclobutanecarboxylic acid ("A61")



Step 1: Ethyl 1-(4-nitrophenyl)cyclobutanecarboxylate



10 g of ethyl 4-nitrophenylacetate are dissolved in in 100 ml of DMF, added dropwise to a suspension of 4.97 g of sodium hydride in 20 ml of DMF with ice-cooling and stirred for 30 min. 6.6 ml of 1,3-dibromopropane are subsequently added, and the mixture is stirred at 23°C for 12 h. The reaction mixture is subsequently stirred into a mixture of 100 ml of 1 N hydrochloric acid

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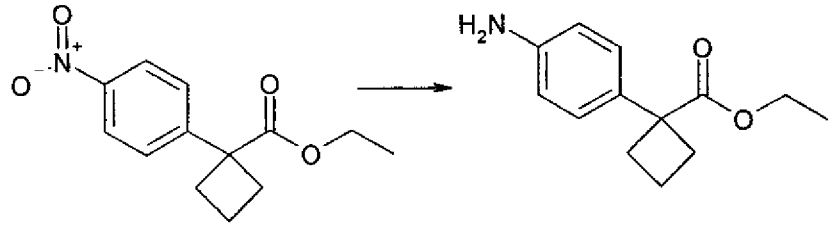
and 200 g of ice. The mixture is washed four times with 100 ml of ethyl acetate each time, the combined organic phases once with 100 ml of sodium chloride solution, dried over sodium sulfate and, after filtration, evaporated to dryness in vacuo. The residue is purified by column chromatography (reversed phase). Yield: 5.5 g (46%) of ethyl 1-(4-nitrophenyl)-cyclobutanecarboxylate; LC-MS retention time: 2.21 min ("nonpolar" gradient);

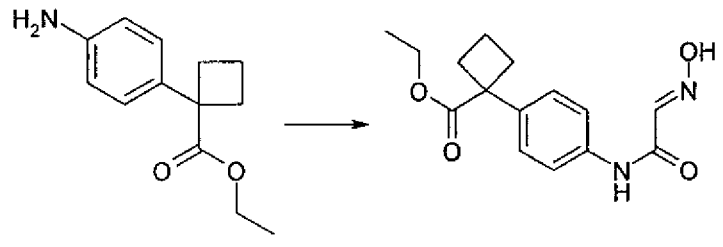
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.22 (d, J = 8.9, 2H), 7.55 (d, J = 8.9, 2H), 4.09 (q, J = 7.1, 2H), 2.86 – 2.76 (m, 2H), 2.58 – 2.47 (m, 2H), 2.11 – 1.99 (m, 1H), 1.93 – 1.80 (m, 1H), 1.13 (t, J = 7.1, 3H).

Step 2: Ethyl 1-(4-aminophenyl)cyclobutanecarboxylate



5.5 g of ethyl 1-(4-nitrophenyl)cyclobutanecarboxylate are dissolved in 55 ml of tetrahydrofuran, 2 g of 5% Pd/C (52.3% of water) are added, and the mixture is stirred at 23°C under a hydrogen atmosphere for 1 h. After aeration, insoluble material is filtered off, and the filtrate is evaporated to dryness in vacuo. Yield: 4.3 g (89%) of ethyl 1-(4-aminophenyl)cyclobutanecarboxylate; LC-MS retention time: 2.05 min ("nonpolar" gradient).

Step 3: Ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenylcyclobutanecarboxylate



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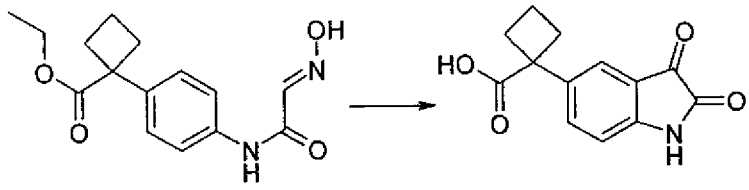
6.25 g of chloral hydrate are dissolved in 180 ml of water, 9.39 g of Na_2SO_4 are added, and the mixture is stirred at 23°C for 10 min. A solution of 6.9 g of ethyl 1-(4-aminophenyl)cyclobutanecarboxylate hydrochloride in 50 ml of water is added to this solution. 7.65 g of hydroxylammonium chloride in 20 ml of water are added to the resultant suspension, and the mixture is stirred at 60°C for 5 h. The mixture is subsequently allowed to cool, during which an oil deposits. This mixture is washed three times with 50 ml of dichloromethane each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The mixture obtained is employed in the following reaction without further purification:

Yield: 9.1 g (100%) of ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenyl-cyclobutanecarboxylate; LC-MS retention time: 2.02 min.

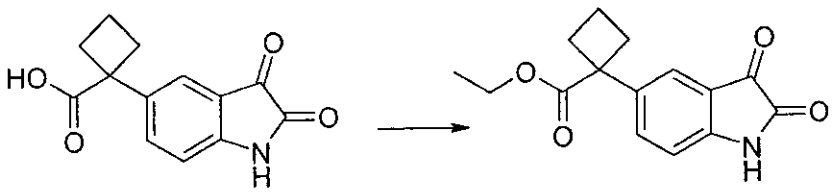
Step 4: 1-(2,3-Dioxoindolin-5-yl))cyclobutanoic acid



8.0 g of ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenylcyclobutane-carboxylate are added in portions to 30 ml of sulfuric acid (98%) at 50°C, during which the temperature rises to 60°C. When the addition is complete, the mixture is stirred at 50°C for a further 120 min and subsequently poured into 400 ml of ice-water. The mixture is washed three times with 200 ml of dichloromethane/ethanol (9:1) each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The crude product obtained is employed in the next reaction without further purification.

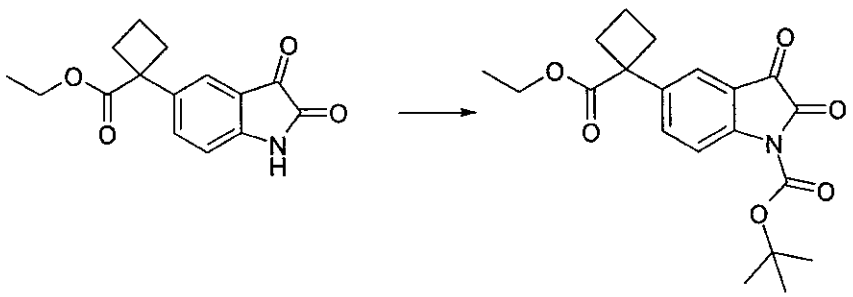
Yield: 7.2 g (100%) of 1-(2,3-dioxoindolin-5-yl)cyclobutanoic acid;
LC-MS retention time: 1.51 min.

Step 5: Ethyl 1-(2,3-dioxoindolin-5-yl))cyclobutanecarboxylate



7.2 g of 1-(2,3-dioxoindolin-5-yl)cyclobutanecarboxylic acid are dissolved in 100 ml of ethanol, and 500 mg of toluene-4-sulfonic acid monohydrate are added. The mixture is heated at 80°C for 1 h and subsequently evaporated in vacuo. The residue is taken up in 100 ml of water and 100 ml of ethyl acetate, and the aqueous phase is separated off. The aqueous phase is washed a further twice with 100 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate, filtered and evaporated to dryness in vacuo. The residue is purified by column chromatography (reversed phase), giving 2.4 g (30%) of ethyl 1-(2,3-dioxoindolin-5-yl)cyclobutanecarboxylate;
LC-MS retention time: 1.99 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.50 (dd, J = 8.2, 2.0, 1H), 7.39 (d, J = 2.0, 1H), 6.94 (d, J = 8.1, 1H), 4.07 (m, 2H), 2.79 – 2.69 (m, 2H), 2.42 (m, 2H), 2.03 – 1.77 (m, 2H), 1.22 – 1.11 (m, 3H).

Step 6: 5-(1-Ethoxycarbonylcyclobutyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline



2.2 g of di-tert-butyl dicarbonate are added to 2.4 g of ethyl 1-(2,3-dioxoindolin-5-yl))cyclobutanoate and 5 mg of 4-dimethylaminopyridine in 50 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 12 h. The mixture is evaporated at 23°C in vacuo and processed further directly. Yield:

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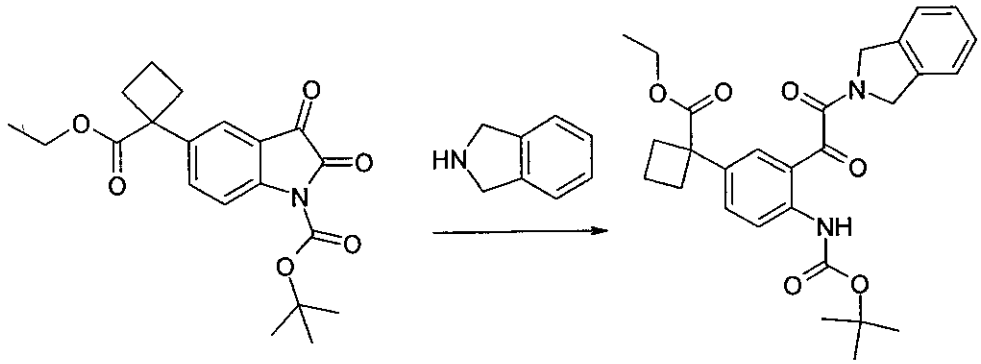
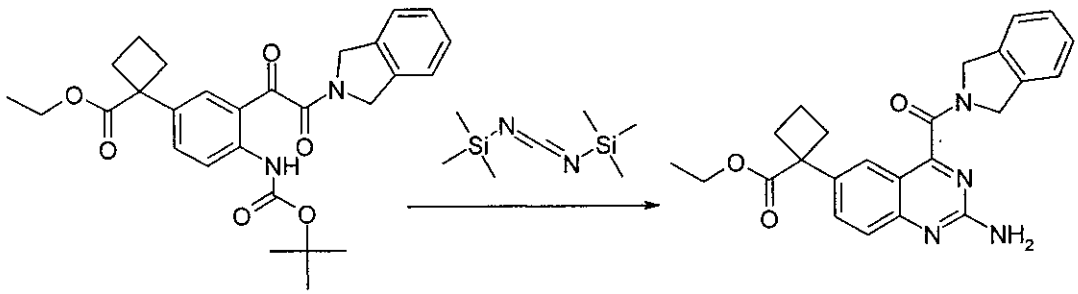
3.3 g (100%) of 5-(1-ethoxycarbonylcyclobutyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline; LC-MS retention time: 2.35 min ("nonpolar" gradient).

Step 7: Ethyl 1-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]cyclobutanecarboxylate



1.049 g of isoindoline are added to 3.3 g of 5-(1-ethoxycarbonylcyclobutyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline in 50 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 1 h. The mixture is evaporated to dryness in vacuo and purified by column chromatography, giving 1.2 g (28%) of ethyl 1-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxoacetyl)-phenyl]-cyclobutanecarboxylate; LC-MS retention time: 2.75 min ("nonpolar" gradient).

Step 8: Ethyl 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclo-butanecarboxylate



1.2 g of ethyl 1-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]cyclobutanecarboxylate are dissolved in 50 ml of acetonitrile under argon. 370 mg of caesium fluoride and 679 µl of bis(trimethylsilyl)carbo-diimide are added to the solution. The mixture is stirred at room temperature

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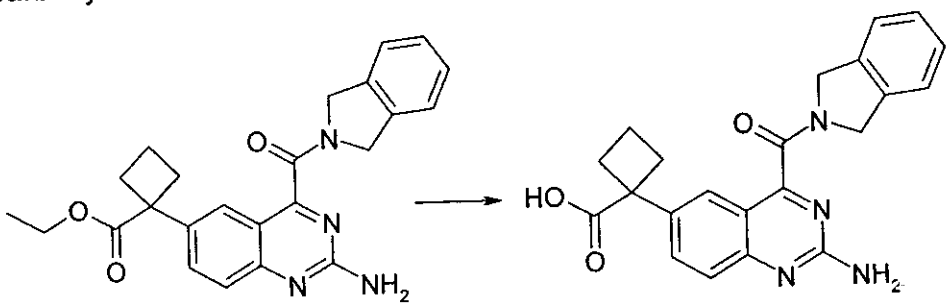
for 15 min, and 6 ml of hydrochloric acid (1N) are then added, and the mixture is neutralised using bicarbonate. The aqueous phase is washed 3 times with 100 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate, filtered and evaporated to dryness in vacuo. Yield: 1 g (99%) of ethyl 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclobutanecarboxylate (oil);
LC-MS retention time: 1.75 min ("nonpolar" gradient).

Step 9: 1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclobutanecarboxylic acid



1.0 g of ethyl 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclobutanecarboxylate are dissolved in 15 ml of tetrahydrofuran, and 10 ml of 2N sodium hydroxide solution are added. The mixture is stirred at 50°C for 4 h and subsequently evaporated in vacuo. The mixture is then adjusted to pH2 using 3 ml of 25% hydrochloric acid with ice-cooling, with yellow crystals precipitating. The precipitate obtained is filtered off and dried in vacuo. Yield: 800 mg (86%) of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclobutanecarboxylic acid; LC-MS retention time: 1.32 min.

Example 9

Preparation of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylpropanoic acid ("A62")

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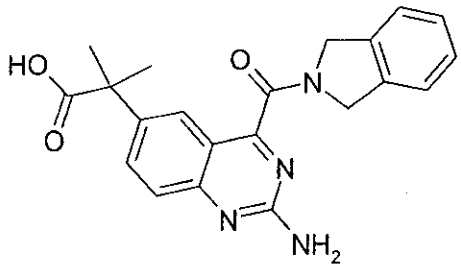
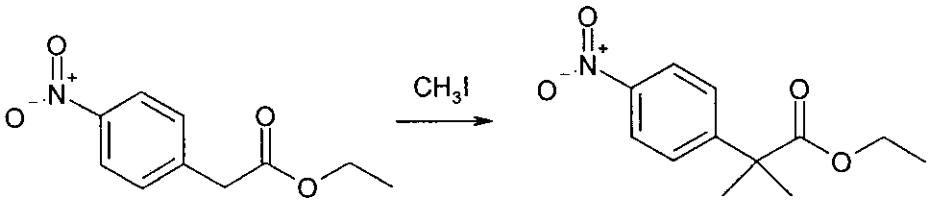
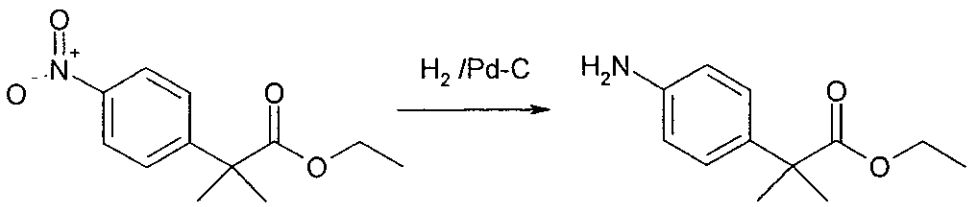


Step 1: Ethyl 2-methyl-2-(4-nitrophenyl)propanoate



10 g of ethyl 4-nitrophenylacetate are dissolved in in 100 ml of DMF, added dropwise to a suspension of 4.97 g of sodium hydride in 20 ml of DMF with ice-cooling and stirred for 30 min. 7.14 ml of methyl iodide are subsequently added, and the mixture is stirred at 23°C for 12 h. The reaction mixture is subsequently stirred into 100 ml of saturated ammonium chloride solution. The mixture is washed four times with 100 ml of ethyl acetate each time, the combined organic phases with 100 ml of sodium chloride solution, dried over sodium sulfate and, after filtration, evaporated to dryness in vacuo. The residue is purified by column chromatography (reversed phase). Yield: 8.2 g (72%) of ethyl 2-methyl-2-(4-nitrophenyl)propanoate; LC-MS retention time: 2.39 min.

Step 2: Ethyl 2-(4-aminophenyl)-2-methylpropanoate



8.7 g of ethyl 2-methyl-2-(4-nitrophenyl)propanoate are dissolved in 90 ml of tetrahydrofuran, 2 g of 5% Pd/C (52.3% of water) are added, and the mixture is stirred at 23°C under a hydrogen atmosphere for 1 h. After aeration, the solid material is filtered off, and the filtrate is evaporated to dryness in vacuo.

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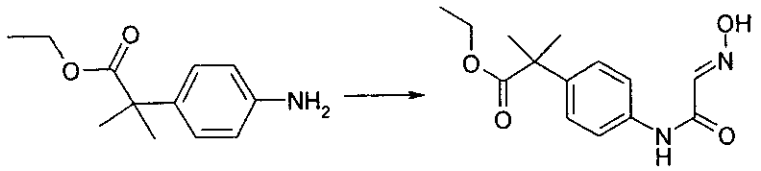
Yield: 7.3 g (97%) of ethyl 2-(4-aminophenyl)-2-methylpropanoate; LC-MS retention time: 2.39 min.

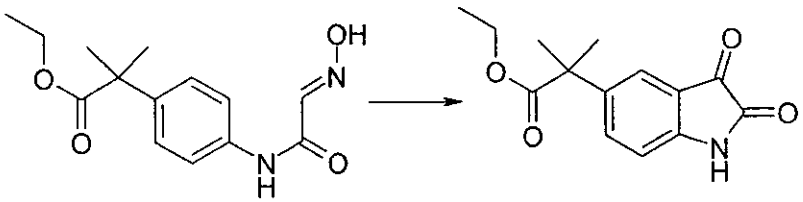
Step 3: Ethyl 2-[4-[[(2E)-2-hydroxyiminoacetyl]amino]phenyl]-2-methyl-propanoate



7.23 g of chloral hydrate are dissolved in 180 ml of water, 10.87 g of Na_2SO_4 are added, and the mixture is stirred at 23°C for 10 min. A solution of 7.55 g of ethyl 2-(4-aminophenyl)-2-methylpropanoate hydrochloride in 50 ml of water is added to this solution. 8.86 g of hydroxylammonium chloride in 20 ml of water are added to the resultant suspension, and the mixture is stirred at 60°C for 5 h. The mixture is subsequently allowed to cool, during which an orange oil deposits. This mixture is washed three times with 50 ml of dichloromethane each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The mixture obtained is employed in the following reaction without further purification.

Yield: 10.0 g (98%) of ethyl 2-[4-[[(2E)-2-hydroxyiminoacetyl]amino]phenyl]-2-methylpropanoate; LC-MS retention time: 1.92 min.

Step 4: Ethyl 2-(2,3-dioxoindolin-5-yl)-2-methylpropanoate



8.0 g of ethyl 2-[4-[[(2E)-2-hydroxyiminoacetyl]amino]phenyl]-2-methyl-propanoate are added in portions to 30 ml of sulfuric acid (98%) at 50°C, during which the temperature rises to 60°C. When the addition is complete, the mixture is stirred at 50°C for a further 120 min and subsequently poured into 400 ml of ice-water. The mixture is washed three times with 200 ml of

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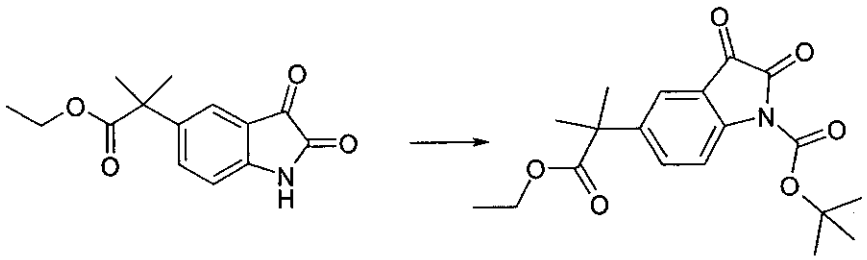
dichloromethane/ethanol (9:1) each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The crude product obtained is employed in the next reaction without further purification. Yield: 7.2 g (100%) of ethyl 2-(2,3-dioxoindolin-5-yl)-2-methylpropanoate obtained; LC-MS retention time: 1.80 min;
^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.56 (dd, J = 8.4, 2.1, 1H), 7.45 (d, J = 1.8, 1H), 6.92 (d, J = 8.2, 1H), 4.08 (q, J = 7.0, 2H), 1.51 (s, 6H), 1.14 (t, J = 7.1, 3H).

Step 5: 5-(2-Ethoxy-1,1-dimethyl-2-oxoethyl))-1-tert-butoxycarbonyl-2,3-dioxoindoline



2.51 g of di-tert-butyl dicarbonate are added to 3.0 g of ethyl 2-(2,3-dioxoindolin-5-yl)-2-methylpropanoate and 50 mg of 4-dimethylaminopyridine in 50 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 12 h. The mixture is evaporated at 23°C in vacuo and processed further directly. Yield: 4.1 g (99%) of 5-(2-ethoxy-1,1-dimethyl-2-oxoethyl))-1-tert-butoxycarbonyl-2,3-dioxoindoline; LC-MS retention time: 2.25 min ("nonpolar" gradient).

Step 6: Ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]-2-methylpropanoate

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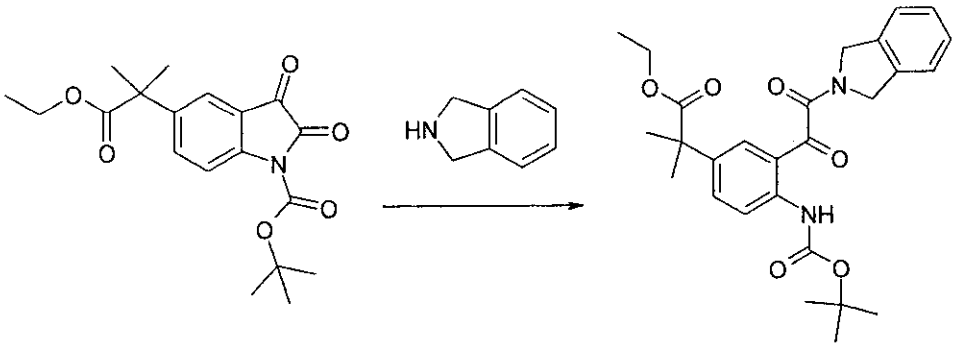
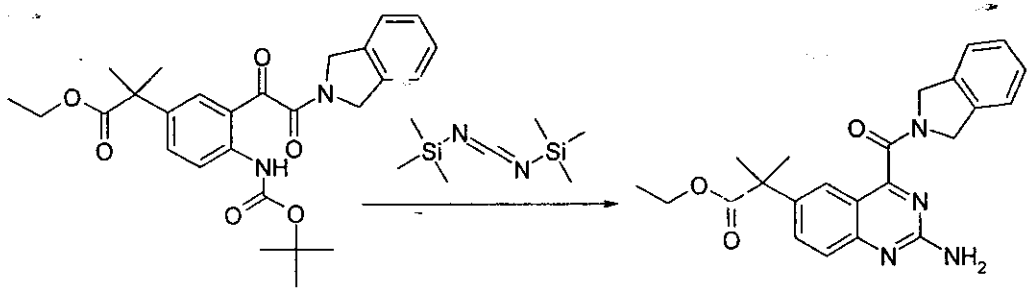


1.368 g of isoindoline are added to 4.15 g of 5-(2-ethoxy-1,1-dimethyl-2-oxo-ethyl))-1-tert-butoxycarbonyl-2,3-dioxoindoline in 50 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 1 h. The mixture is evaporated to dryness in vacuo and purified by column chromatography, giving 3.2 g (58%) of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]-2-methylpropanoate; LC-MS retention time: 2.68 min ("non-polar" gradient).

Step 7: Ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylpropanoate



3.2 g of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxoacetyl)-phenyl]-2-methylpropanoate are dissolved in 100 ml of acetonitrile under argon. 1.012 g of caesium fluoride and 1.81 ml of bis(trimethylsilyl)carbo-diimide are added to the solution. The mixture is stirred at room temperature for 15 min, and 14 ml of hydrochloric acid (1N) are then added, and the mixture is neutralised using bicarbonate. The aqueous phase is washed three times with 100 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate, filtered and evaporated to dryness in vacuo.

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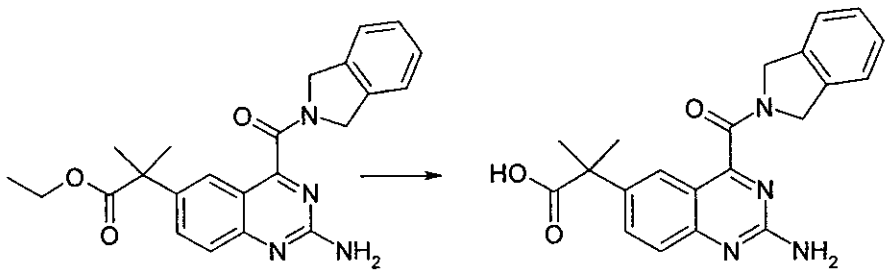
Yield: 2.4 g (89%) of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylpropanoate (oil);
LC-MS retention time: 2.29 min ("nonpolar" gradient).

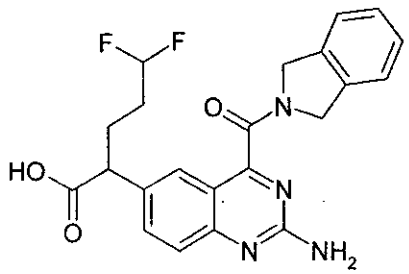
Step 8: 2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methyl-propanoic acid



2.4 g of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methyl-propanoate are dissolved in 40 ml of tetrahydrofuran, and 25 ml of 2N sodium hydroxide solution are added. The mixture is stirred at 50°C for 4 h and subsequently evaporated in vacuo. The mixture is then adjusted to pH2 using 7 ml of 25% hydrochloric acid with ice-cooling, with yellow crystals precipitating. The precipitate obtained is filtered off and dried in vacuo. Yield: 2.0 g (90%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylpropanoic acid;
LC-MS retention time: 1.23 min ("nonpolar" gradient).

Example 10

Preparation of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5,5-difluoropentanoic acid ("A63")



Step 1: Ethyl 2-(4-aminophenyl)-5,5-difluoropent-4-enoate and ethyl 4-aminophenyl)-2-(3,3-difluoroallyl)-5,5-difluoropent-4-enoate

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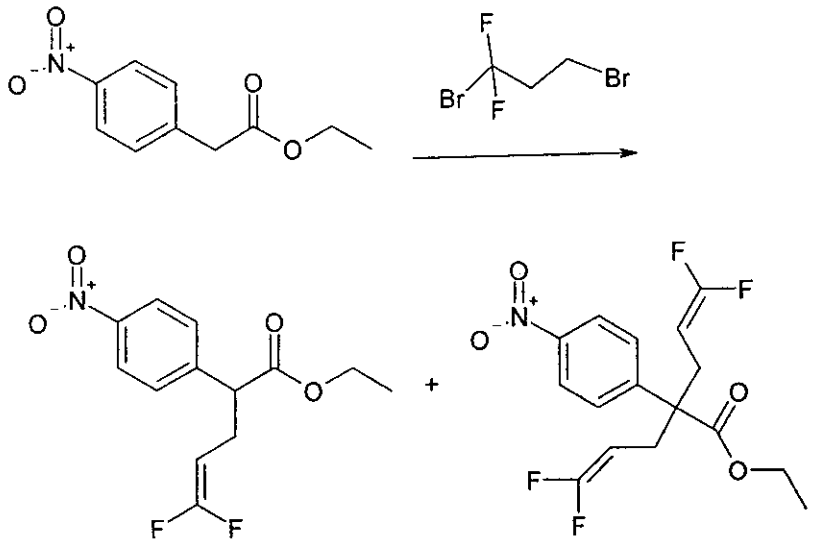

7.113 g of ethyl 4-nitrophenylacetate are dissolved in 60 ml of DMF, added dropwise to a suspension of 3.4 g of sodium hydride in 40 ml of DMF with ice-cooling and stirred for 30 min. 8.8 g of 1,3-dibromo-1,1,-difluoropropane are subsequently added, and the mixture is stirred at 23°C for 12 h. The reaction mixture is subsequently stirred into 100 ml of saturated ammonium chloride solution. The mixture is washed four times with 100 ml of ethyl acetate each time, the combined organic phases with 100 ml of sodium chloride solution, dried over sodium sulfate and, after filtration, evaporated to dryness in vacuo. The residue is purified by column chromatography (reversed phase). Yield: 5.4 g (56%) of ethyl 2-(4-aminophenyl)-5,5-difluoropent-4-enoate; LC-MS retention time: 2.21 min ("nonpolar" gradient);

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.26 – 8.22 (m, 2H), 7.60 – 7.53 (m, 2H), 4.18 (q, J = 7.1, 2H), 2.82 – 2.68 (m, 3H), 1.99 (s, 1H), 1.17 (t, J = 7.1, 3H);

and 2.4 g (25%) of ethyl 4-aminophenyl)-2-(3,3-difluoroallyl)-5,5-difluoropent-4-enoate; LC-MS retention time: 2.49 min ("nonpolar" gradient);

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.25 – 8.19 (m, 2H), 7.63 – 7.57 (m, 2H), 4.04 (q, J = 7.2, 2H), 2.74 – 2.64 (m, 1H), 2.51 (dt, J = 3.7, 1.8, 2H), 2.49 – 2.39 (m, 1H), 1.18 (t, J = 7.2, 2H), 1.14 (t, J = 7.1, 3H).

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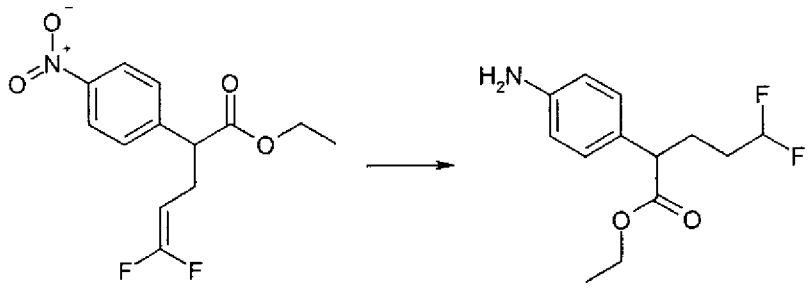
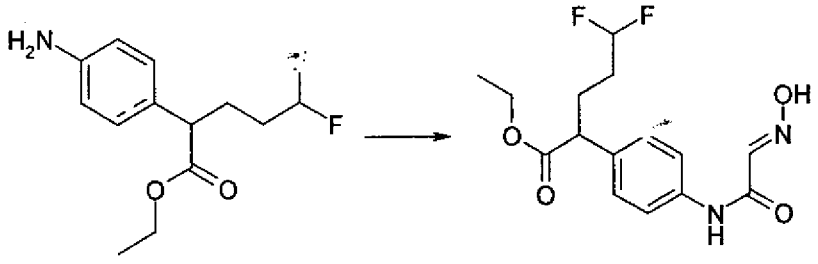
Step 2: Ethyl 2-(4-aminophenyl-5,5-difluoropentanoate



5.4 g of ethyl 2-(4-aminophenyl)-5,5-difluoropent-4-enoate are dissolved in 60 ml of tetrahydrofuran, 2 g of 5% Pd/C (52.3% of water) are added, and the mixture is stirred at 23°C under a hydrogen atmosphere for 1 h. After aeration, the solid material is filtered off, and the filtrate is evaporated to dryness in vacuo. Yield: 5.0 g (99%) of ethyl 2-(4-aminophenyl-5,5-difluoropentanoate; LC-MS retention time: 1.67 min.

Step 3: Ethyl 5,5-difluoro-2-[4-[[(2E)-2-hydroxyiminoacetyl]amino]phenyl]-pentanoate



3.804 g of chloral hydrate are dissolved in 40 ml of water, 5.68 g of Na_2SO_4 are added, and the mixture is stirred at 23°C for 10 min. A solution of 5.0 g of ethyl 2-(4-aminophenyl-5,5-difluoropentanoate hydrochloride in 40 ml of water is added to this solution. 4.169 g of hydroxylammonium chloride in 20 ml of water are added to the resultant suspension, and the mixture is stirred at 60°C for 5 h. The mixture is subsequently allowed to cool, during which an orange oil deposits. This mixture is washed three times with 50 ml of dichloromethane each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The mixture obtained was employed in the following reaction without further purification. Yield: 5.0 g (78%) of ethyl

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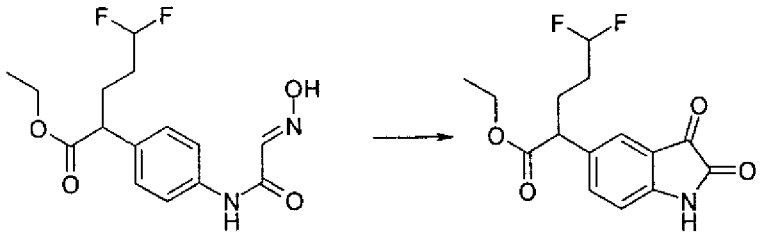
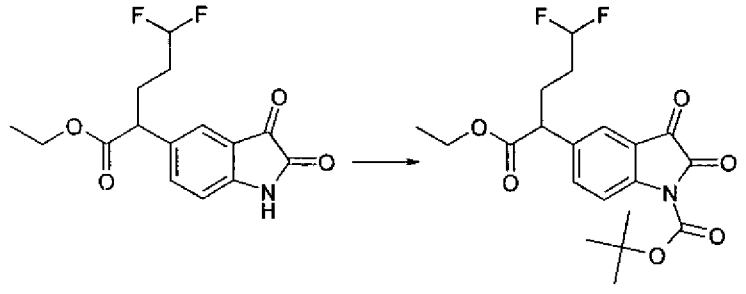
5,5-difluoro-2-[4-[[(2E)-2-hydroxyiminoacetyl]amino]phenyl]pentanoate; LC-MS retention time: 1.99 min.

Step 4: Ethyl 2-(2,3-dioxoindolin-5-yl)-5,5-difluoropentanoate



6.0 g of ethyl 5,5-difluoro-2-[4-[[(2E)-2-hydroxyiminoacetyl]amino]phenyl]-pentanoate are added in portions to 30 ml of sulfuric acid (98%) at 50°C, during which the temperature rises to 60°C. When the addition is complete, the mixture is stirred at 50°C for a further 120 min and subsequently poured into 200 ml of ice-water. The mixture is washed three times with 200 ml of dichloromethane/ethanol (9:1) each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The crude product obtained is employed in the next reaction without further purification. Yield: 4.2 g (74%) of ethyl 2-(2,3-dioxoindolin-5-yl)-5,5-difluoropentanoate; LC-MS retention time: 1.95 min

Step 5: 5-(1-Ethoxycarbonyl-4,4-difluorobutyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline



3.71 g of di-tert-butyl dicarbonate are added to 4.0 g of ethyl 2-(2,3-dioxo-indolin-5-yl)-5,5-difluoropentanoate and 50 mg of 4-dimethylaminopyridine in 50 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 12 h. The mixture is evaporated at 23°C in vacuo and processed further

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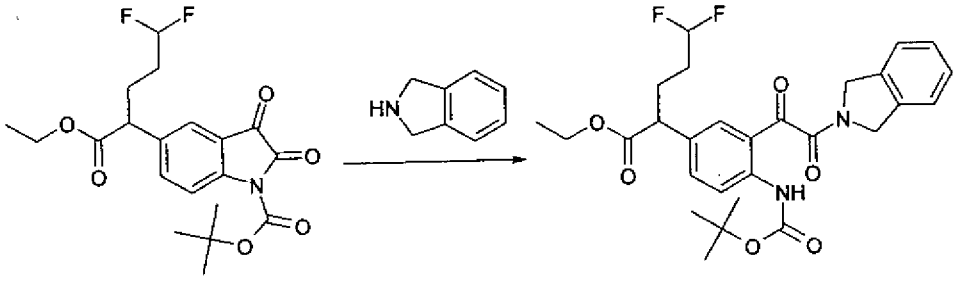
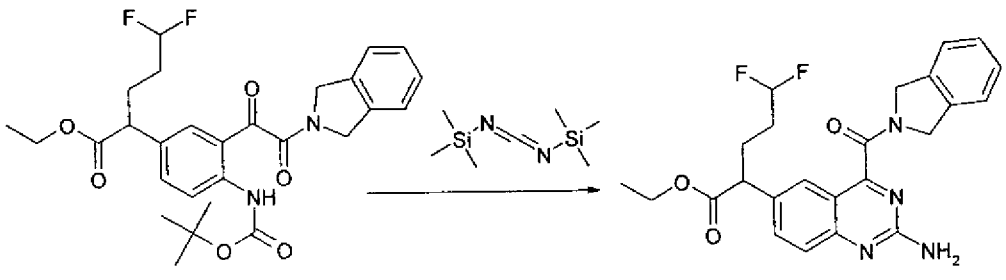
directly. Yield: 5.3 g (99%) of 5-(1-ethoxycarbonyl-4,4-difluorobutyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline; LC-MS retention time: 2.24 min ("nonpolar" gradient).

Step 6: Ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]-5,5-difluoropentanoate



1.53 g of isoindoline are added to 5.29 g of 5-(1-ethoxycarbonyl-4,4-difluoro-butyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline in 50 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 1 h. The mixture is evaporated to dryness in vacuo and purified by column chromatography, giving 1.7 g (25%) of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]-5,5-difluoropentanoate; LC-MS retention time: 2.62 min ("non-polar" gradient).

Step 7: Ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5,5-difluoropentanoate



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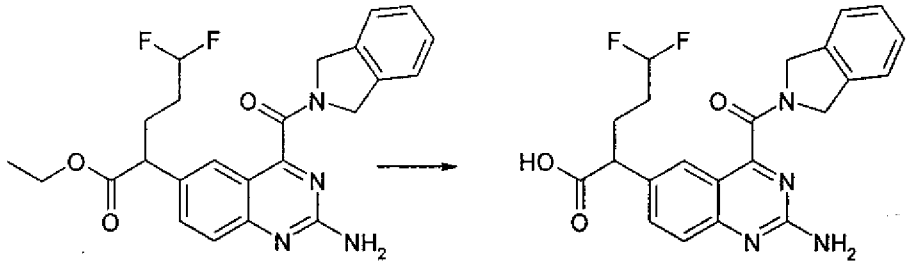
1.7 g of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxoacetyl)-phenyl]-5,5-difluoropentanoate are dissolved in 50 ml of acetonitrile under argon. 486 mg of caesium fluoride and 869 µl of bis(trimethylsilyl)carbodiimide are added to the solution. The mixture is stirred at room temperature for 15 min, and 6 ml of hydrochloric acid (1N) are then added, and the mixture is neutralised using bicarbonate. The aqueous phase is washed three times with 100 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate, filtered and evaporated to dryness in vacuo. Yield: 1.4 g (96%) of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5,5-difluoropentanoate (oil); LC-MS retention time: 1.71min ("nonpolar" gradient).

Step 8: 2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5,5-difluoro-pentanoic acid



1.2 g of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5,5-difluoropentanoate are dissolved in 15 ml of tetrahydrofuran, and 10 ml of 2N sodium hydroxide solution are added. The mixture is stirred at 50°C for 4 h and subsequently evaporated in vacuo. The mixture is then adjusted to pH2 using 25% hydrochloric acid with ice-cooling, with yellow crystals precipitating. The precipitate obtained is filtered off and dried in vacuo. Yield: 800 mg (71%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5,5-difluoropentanoic acid; LC-MS retention time: 1.35 min ("nonpolar" gradient).

Example 11

Preparation of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]pentanoic acid ("A64")

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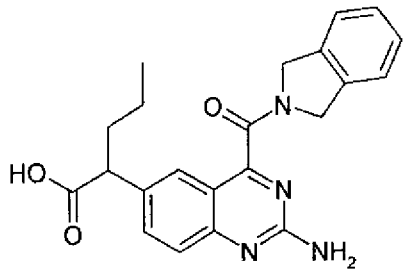
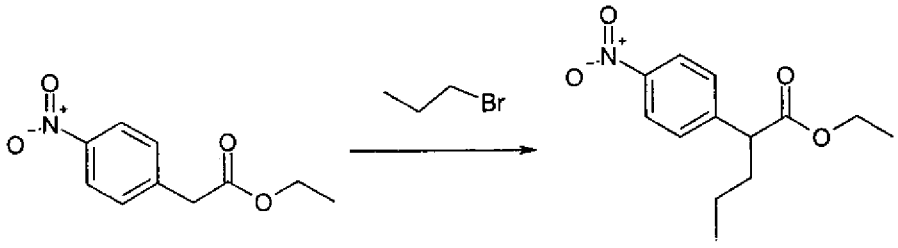
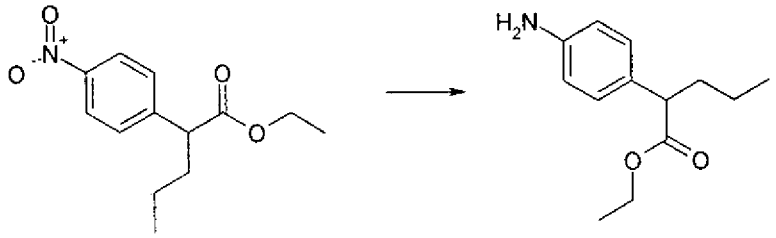


Step 1: Ethyl 2-(4-nitrophenyl)pentanoate



6.694 g of ethyl 4-nitrophenylacetate are dissolved in 30 ml of DMF, added dropwise to a suspension of 1.4 g of sodium hydride in 30 ml of DMF with ice-cooling and stirred for 30 min. 2.91 ml of 1-bromopropane in 20 ml of DMF are subsequently added, and the mixture is stirred at 23°C for 12 h. The reaction mixture is subsequently stirred into 100 ml of saturated ammonium chloride solution. The mixture is washed four times with 100 ml of ethyl acetate each time, the combined organic phases with 100 ml of sodium chloride solution, dried over sodium sulfate and, after filtration, evaporated to dryness in vacuo. The residue is purified by column chromatography (reversed phase). Yield: 5.3 g (66%) of ethyl 2-(4-nitrophenyl)pentanoate; LC-MS retention time: 2.28 min ("nonpolar" gradient).

Step 2: Ethyl 2-(4-aminophenyl)pentanoate



5.3 g of ethyl 2-(4-nitrophenyl)pentanoate are dissolved in 55 ml of tetra-hydrofuran, 1 g of 5% Pd/C (52.3% of water) is added, and the mixture is

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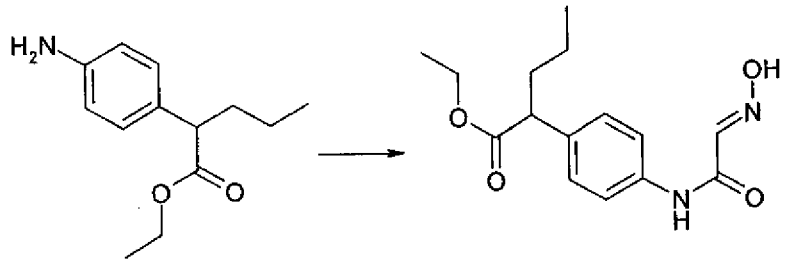
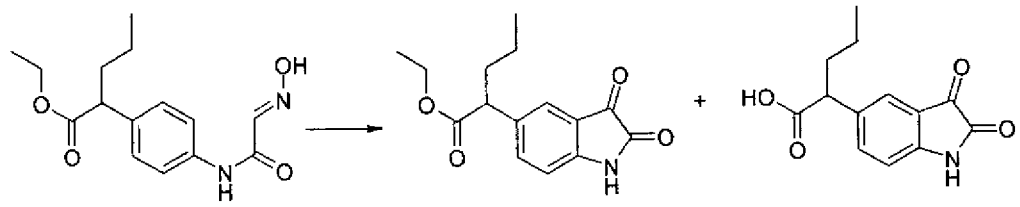
stirred at 23°C under a hydrogen atmosphere for 1 h. After aeration, the solid material is filtered off, and the filtrate is evaporated to dryness in vacuo. Yield: 4.7 g (99%) of ethyl 2-(4-aminophenyl)pentanoate (oil); LC-MS retention time: 1.40 min ("nonpolar" gradient).

Step 3: Ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenyl]pentanoate



4.135 g of chloral hydrate are dissolved in 50 ml of water, 6.11 g of Na_2SO_4 are added, and the mixture is stirred at 23°C for 10 min. A solution of 4.7 g of ethyl 2-(4-aminophenyl)pentanoate hydrochloride in 50 ml of water is added to this solution. 5.11 g of hydroxylammonium chloride in 20 ml of water are added to the resultant suspension, and the mixture is stirred at 60°C for 5 h. The mixture is subsequently allowed to cool, during which an orange oil deposits. This mixture is washed three times with 50 ml of dichloromethane each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The mixture obtained is employed in the following reaction without further purification.
Yield: 5.2 g (78%) of ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenyl]-pentanoate; LC-MS retention time: 1.76 min ("nonpolar" gradient).

Step 4: Ethyl 2-(2,3-dioxoindolin-5-yl)pentanoate



30 ml of sulfuric acid (98%) are added in portions to 6.2 g of ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenyl]pentanoate, during which the

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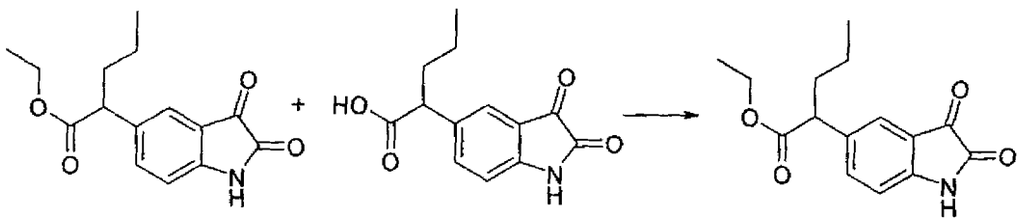
temperature rises to 60°C. When the addition is complete, the mixture is stirred at 50°C for a further 120 min and subsequently poured into 400 ml of ice-water. The mixture is washed three times with 200 ml of dichloromethane/ ethanol (9:1) each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The crude product obtained is employed in the next reaction without further purification. Yield: 5.3 g (mixture of ethyl 2-(2,3-dioxoindolin-5-yl)pentanoate and 2-(2,3-dioxo-indolin-5-yl)pentanoic acid in the ratio 20 : 80); LC-MS retention time: 2.08 min (ester) and 1.62 min (acid).

Step 5: Ethyl 2-(2,3-dioxoindolin-5-yl)pentanoate



The resultant mixture of ethyl 2-(2,3-dioxoindolin-5-yl)pentanoate and 2-(2,3-dioxoindolin-5-yl)pentanoic acid (5.3 g) from the preceding reaction is dissolved in 100 ml of ethanol and stirred at 70°C for 4 h together with 500 mg of toluene-4-sulfonic acid. The mixture is subsequently evaporated in vacuo, taken up in 50 ml of ethyl acetate and washed with 50 ml of water. The organic phase is dried over sodium sulfate, filtered off and evaporated to dryness. Yield: 5.5 g (94%) of ethyl 2-(2,3-dioxoindolin-5-yl)pentanoate; LC-MS retention time: 2.08 min.

Step 6: 5-(1-Ethoxycarbonylbutyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline

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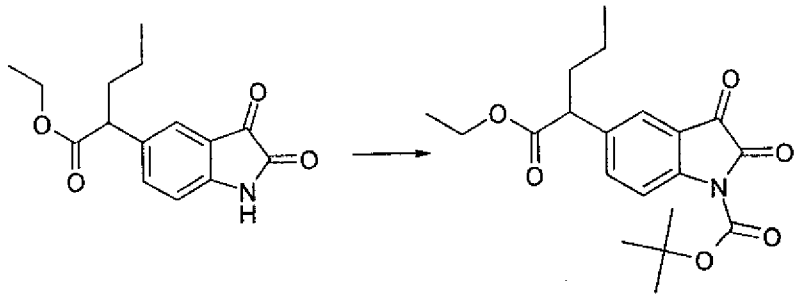
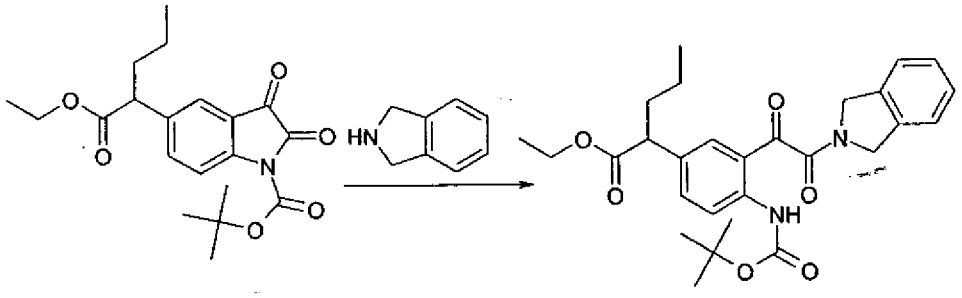


4.80 g of di-tert-butyl dicarbonate are added to 5.5 g of ethyl 2-(2,3-dioxo-indolin-5-yl)pentanoate and 50 mg of 4-dimethylaminopyridine in 100 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 12 h. The mixture is evaporated at 23°C in vacuo and processed further directly. Yield: 7.3 g (99%) of 5-(1-ethoxycarbonylbutyl)-1-tert-butoxycarbonyl-2,3-dioxo-indoline; LC-MS retention time: 2.42 min ("nonpolar" gradient).

Step 7: Ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]pentanoate



1.12 g of isoindoline are added to 3.5 g of 5-(1-ethoxycarbonylbutyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline in 50 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 1 h. The mixture is evaporated to dryness in vacuo and purified by column chromatography, giving 1.4 g (30%) of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxoacetyl)phenyl]-pentanoate; LC-MS retention time: 2.78 min ("nonpolar" gradient).

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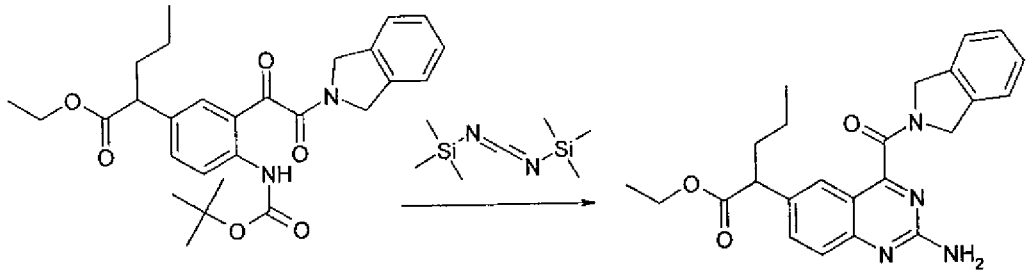
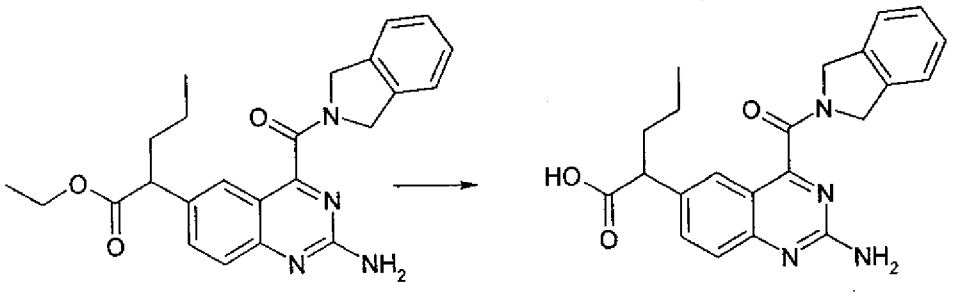
Step 8: Ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-pentanoate



1.4 g of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxoacetyl)-phenyl]pentanoate are dissolved in 50 ml of acetonitrile under argon. 431 mg of caesium fluoride and 769 µl of bis(trimethylsilyl)carbodiimide are added to the solution. The mixture is stirred at room temperature for 15 min, and 6 ml of hydrochloric acid (1N) are then added, and the mixture is neutralised using bicarbonate. The aqueous phase is washed three times with 100 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate, filtered and evaporated to dryness in vacuo. Yield: 1.1 g (92%) of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]pentanoate (oil); LC-MS retention time: 1.84 min ("nonpolar" gradient).

Step 9: 2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]pentanoic acid



1.2 g of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]pentanoate are dissolved in 15 ml of tetrahydrofuran, and 10 ml of 2N sodium hydroxide solution are added. The mixture is stirred at 50°C for 4 h and subsequently evaporated in vacuo. The mixture is then adjusted to pH2 using 25% hydro-

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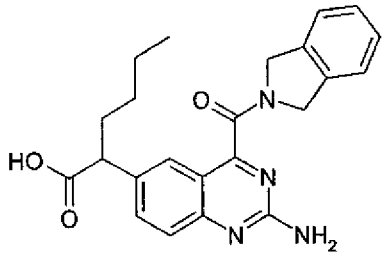
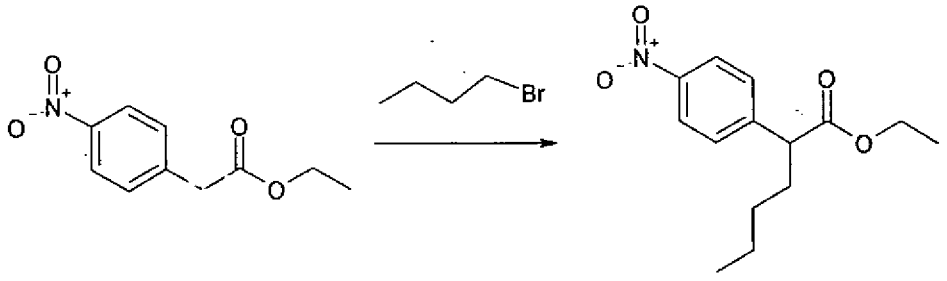
chloric acid with ice-cooling, with yellow crystals precipitating. The precipitate obtained is filtered off and dried in vacuo. Yield: 800 mg (72%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]pentanoic acid; LC-MS retention time: 1.40 min ("nonpolar" gradient).

Example 12

Preparation of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]hexanoic acid ("A65")



Step1: Ethyl 2-(4-nitrophenyl)hexanoate



10.46 g of ethyi 4-nitrophenylacetate are dissolved in 30 ml of DMF, added dropwise to a suspension of 2.0 g of sodium hydride in 20 ml of DMF with ice-cooling and stirred for 30 min. 5.394 ml of 1-bromobutane in 20 ml of DMF are subsequently added, and the mixture is stirred at 23°C for 12 h. The reaction mixture is subsequently stirred into 100 ml of saturated ammonium chloride solution. The mixture is washed 4 times with 100 ml of ethyl acetate each time, the combined organic phases with 100 ml of sodium chloride solution, dried over sodium sulfate and, after filtration, evaporated to dryness in vacuo. The residue is purified by column chromatography (reversed phase). Yield: 11 g (83%) of ethyl 2-(4-nitrophenyl)hexanoate; LC-MS retention time: 2.44 min ("nonpolar" gradient).

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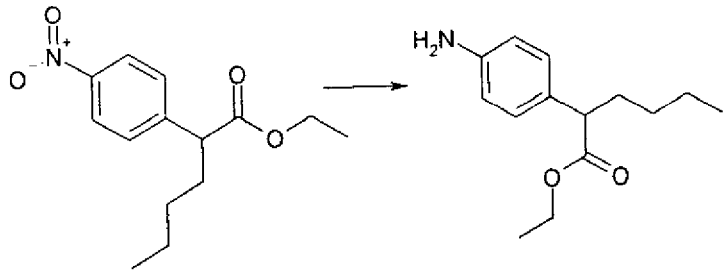
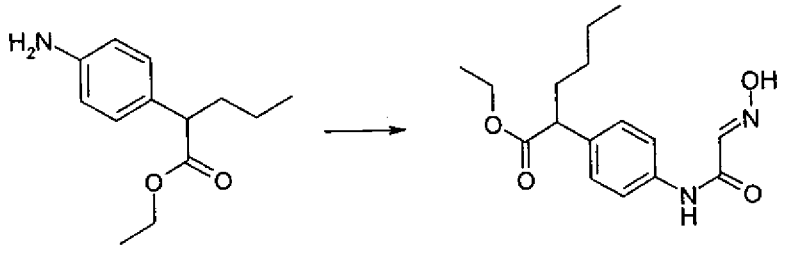
Step 2: Ethyl 2-(4-aminophenyl)hexanoate



5.5 g of ethyl 2-(4-nitrophenyl)hexanoate are dissolved in 55 ml of tetrahydrofuran, 1 g of 5% Pd/C (52.3% of water) is added, and the mixture is stirred at 23°C under a hydrogen atmosphere for 1 h. After aeration, the solid material is filtered off, and the filtrate is evaporated to dryness in vacuo. Yield: 4.8 g (99%) of ethyl 2-(4-aminophenyl)hexanoate (oil); LC-MS retention time: 1.73 min ("nonpolar" gradient).

Step 3: Ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenyl]hexanoate



4.135 g of chloral hydrate are dissolved in 50 ml of water, 6.11 g of Na_2SO_4 are added, and the mixture is stirred at 23°C for 10 min. A solution of 4.8 g of ethyl 2-(4-aminophenyl)hexanoate hydrochloride in 50 ml of water is added to this solution. 5.11 g of hydroxylammonium chloride in 20 ml of water are added to the resultant suspension, and the mixture is stirred at 60°C for 5 h. The mixture is subsequently allowed to cool, during which an orange oil deposits. This mixture is washed three times with 50 ml of dichloromethane each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The mixture obtained is employed in the following reaction without further purification. Yield: 5.0 g (80%) of ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenyl]hexanoate;

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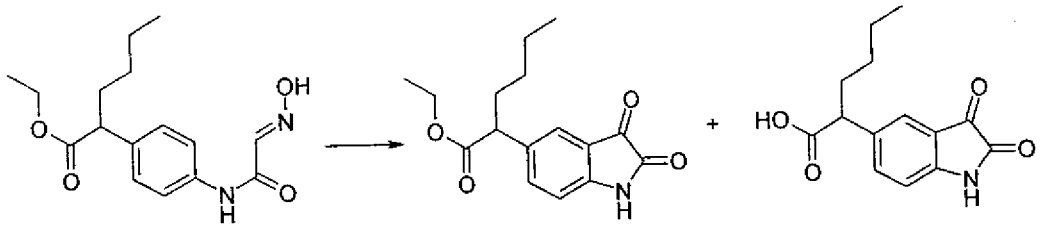
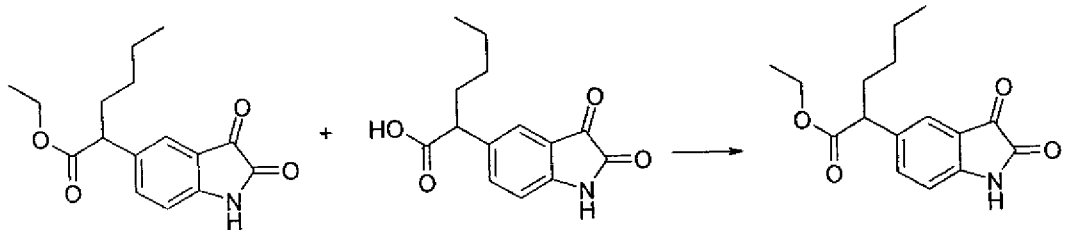
LC-MS retention time: 1.92 min ("nonpolar" gradient).

Step 4: Ethyl 2-(2,3-dioxoindolin-5-yl)hexanoate



30 ml of sulfuric acid (98%) are added in portions to 6.2 g of ethyl 2-[4-[[(2Z/E)-2-hydroxyiminoacetyl]amino]phenyl]hexanoate, during which the temperature rises to 60°C. When the addition is complete, the mixture is stirred at 50°C for a further 120 min and subsequently poured into 400 ml of ice-water. The mixture is washed three times with 200 ml of dichloromethane/ ethanol (9:1) each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The crude product obtained is employed in the next reaction without further purification. Yield: 5.6 g (mixture of ethyl 2-(2,3-dioxoindolin-5-yl)hexanoate and 2-(2,3-dioxoindolin-5-yl)hexanoic acid in the ratio 1 : 3.5); LC-MS retention time: 1.89 min (ester) and 1.35 min (acid) ("nonpolar" gradient).

Step 5: Ethyl 2-(2,3-dioxoindolin-5-yl)hexanoate



The resultant mixture of ethyl 2-(2,3-dioxoindolin-5-yl)hexanoate and 2-(2,3-dioxoindolin-5-yl)pentanoic acid (5.6 g) from the preceding reaction is dissolved in 100 ml of ethanol and stirred at 70°C for 4 h together with 500 mg of toluene-4-sulfonic acid. The mixture is subsequently evaporated in vacuo, taken up in 50 ml of ethyl acetate and washed with 50 ml of water. The organic phase is dried over sodium sulfate, filtered off and evaporated to dryness.

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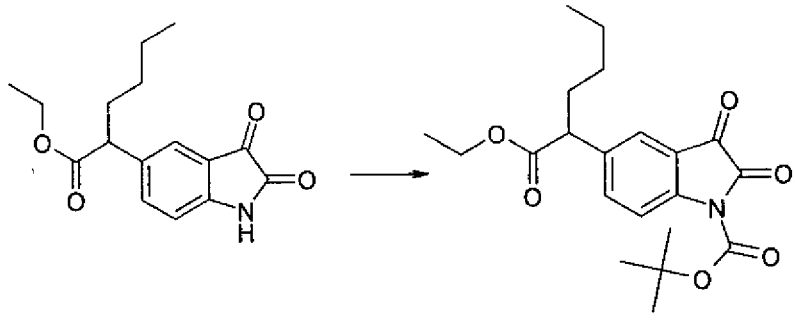
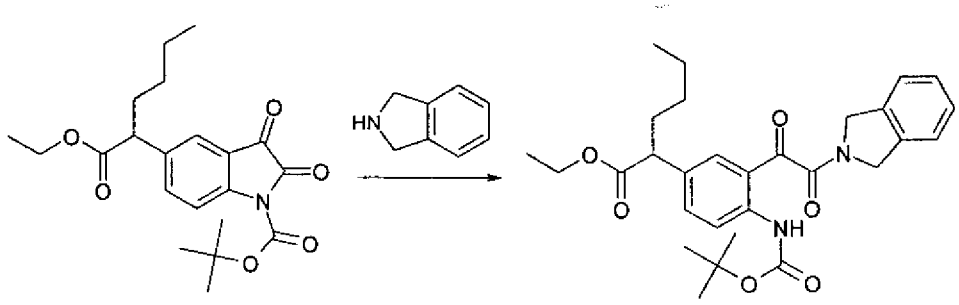
Yield: 4.8 g (79%) of ethyl 2-(2,3-dioxoindolin-5-yl)hexanoate; LC-MS retention time: 1.89 min ("nonpolar" gradient).

Step 6: 5-(1-Ethoxycarbonylpentyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline



3.93 g of di-tert-butyl dicarbonate are added to 4.75 g of ethyl 2-(2,3-dioxo-indolin-5-yl)hexanoate and 50 mg of 4-dimethylaminopyridine in 100 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 12 h. The mixture is evaporated at 23°C in vacuo and processed further directly. Yield: 6.4 g (99%) of 5-(1-ethoxycarbonylpentyl)-1-tert-butoxycarbonyl-2,3-dioxo-indoline; LC-MS retention time: 2.55 min ("nonpolar" gradient).

Step 7: Ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]hexanoate



1.95 g of isoindoline are added to 6.4 g of 5-(1-ethoxycarbonylpentyl)-1-tert-butoxycarbonyl-2,3-dioxoindoline in 100 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 1 h. The mixture is evaporated to dryness in vacuo and purified by column chromatography, giving 3.8 g (46%) of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxoacetyl)phenyl]hexan-oate; LC-MS retention time: 2.89 min ("nonpolar" gradient).

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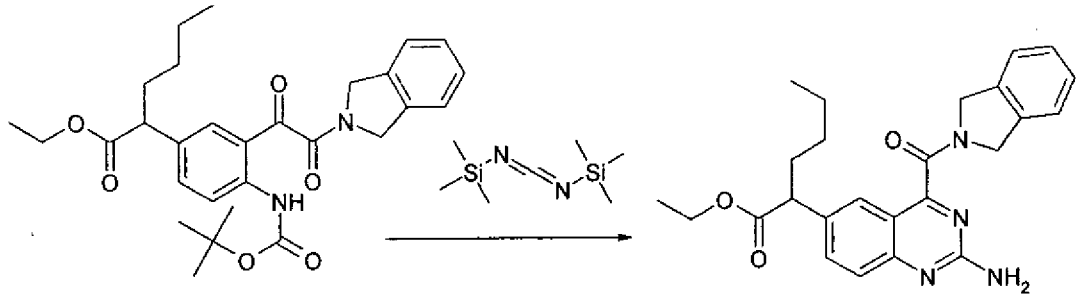
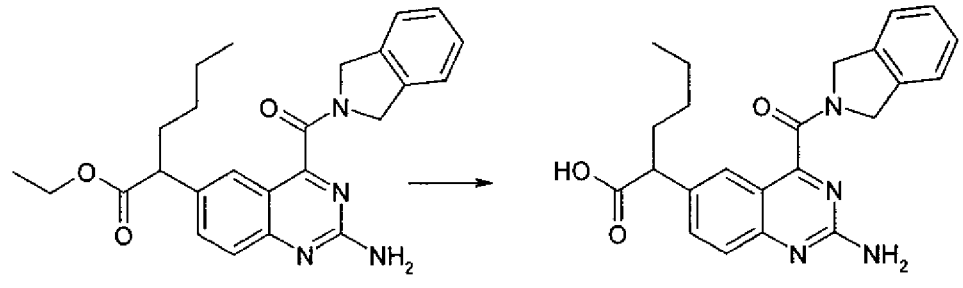
Step 8: Ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]hexanoate



3.8 g of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxoacetyl)-phenyl]hexanoate are dissolved in 100 ml of acetonitrile under argon. 1.12 g of caesium fluoride and 2.01 ml of bis(trimethylsilyl)carbodiimide are added to the solution. The mixture is stirred at room temperature for 15 min, and 6 ml of hydrochloric acid (1N) are then added, and the mixture is neutralised using bicarbonate. The aqueous phase is washed three times with 100 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate, filtered and evaporated to dryness in vacuo. Yield: 3.2 g (99%) of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]hexanoate (oil);
LC-MS retention time: 1.92 min ("nonpolar" gradient).

Step 9: 2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]hexanoic acid



1.0 g of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]hexanoate are dissolved in 15 ml of tetrahydrofuran, and 10 ml of 2N sodium hydroxide solution are added. The mixture is stirred at 50°C for 4 h and subsequently evaporated in vacuo. The mixture is then adjusted to pH2 using 25% hydrochloric acid with ice-cooling, with yellow crystals precipitating. The precipitate

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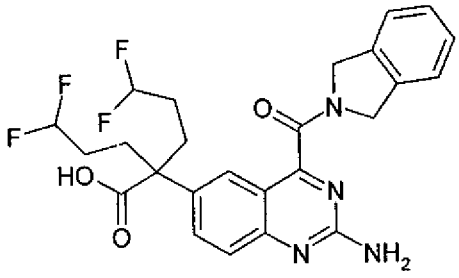
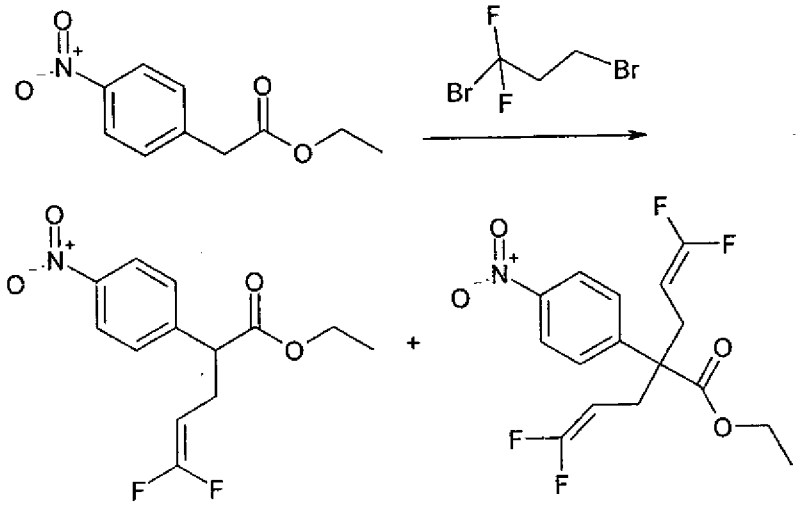
obtained is filtered off and dried in vacuo. Yield: 550 mg (59%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]hexanoic acid;
LC-MS retention time: 1.52 min ("nonpolar" gradient).

Example 13

Preparation of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-5,5-difluoropentanoic acid ("A66")



Step 1: Ethyl 2-(4-aminophenyl)-5,5-difluoropent-4-enoate and ethyl 4-aminophenyl)-2-(3,3-difluoroallyl)-5,5-difluoropent-4-enoate



7.113 g of ethyl 4-nitrophenylacetate are dissolved in 60 ml of DMF, added dropwise to a suspension of 3.4 g of sodium hydride in 40 ml of DMF with ice-cooling and stirred for 30 min. 8.8 g of 1,3-dibromo-1,1,-difluoropropane are subsequently added, and the mixture is stirred at 23°C for 12 h. The reaction mixture is subsequently stirred into 100 ml of saturated ammonium chloride

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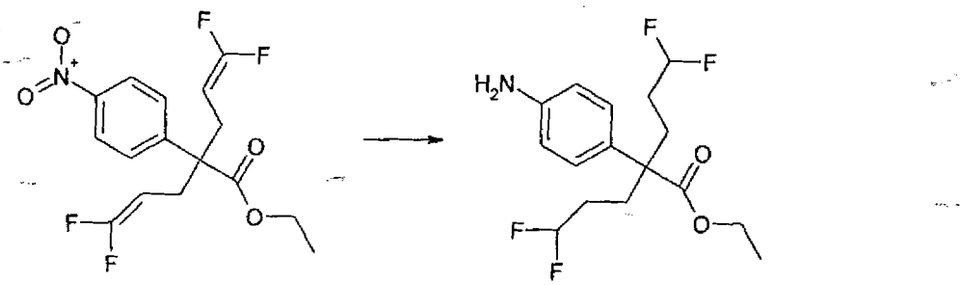
solution. The mixture is washed four times with 100 ml of ethyl acetate each time, the combined organic phases with 100 ml of sodium chloride solution, dried over sodium sulfate and, after filtration, evaporated to dryness in vacuo. The residue is purified by column chromatography (reversed phase). Yield: 5.4 g (56%) of ethyl 2-(4-aminophenyl)-5,5-difluoropent-4-enoate; LC-MS retention time: 2.21 min ("nonpolar" gradient);

^{1}H NMR (400 MHz, DMSO-d_6/TFA-d_1) δ [ppm] 8.26 – 8.22 (m, 2H), 7.60 – 7.53 (m, 2H), 4.18 (q, J = 7.1, 2H), 2.82 – 2.68 (m, 3H), 1.99 (s, 1H), 1.17 (t, J = 7.1, 3H)

and 2.4 g (25%) of ethyl 4-aminophenyl)-2-(3,3-difluoroallyl)-5,5-difluoropent-4-enoate; LC-MS retention time: 2.49 min ("nonpolar" gradient);

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] 8.25 – 8.19 (m, 2H), 7.63 – 7.57 (m, 2H), 4.04 (q, J = 7.2, 2H), 2.74 – 2.64 (m, 1H), 2.51 (dt, J = 3.7, 1.8, 2H), 2.49 – 2.39 (m, 1H), 1.18 (t, J = 7.2, 2H), 1.14 (t, J = 7.1, 3H).

Step 2: Ethyl 2-(4-aminophenyl)-2-(3,3-difluoropropyl)-5,5-difluoropentanoate



2.4 g of ethyl 2-(4-aminophenyl)-2-(3,3-difluoroallyl)-5,5-difluoropent-4-enoate are dissolved in 30 ml of tetrahydrofuran, 1 g of 5% Pd/C (52.3% of water) is added, and the mixture is stirred at 23°C under a hydrogen atmosphere for 1 h. After aeration, the solid material is filtered off, and the filtrate is evaporated to dryness in vacuo. Yield: 2.3 g (99%) of ethyl 2-(4-aminophenyl)-2-(3,3-difluoropropyl)-5,5-difluoropentanoate; LC-MS retention time: 2.09 min.

Step 3: Ethyl 2-(3,3-difluoropropyl)-5,5-difluoro-2-[4-[[(2E)-2-hydroxyimino-acetyl]amino]phenyl] pentanoate

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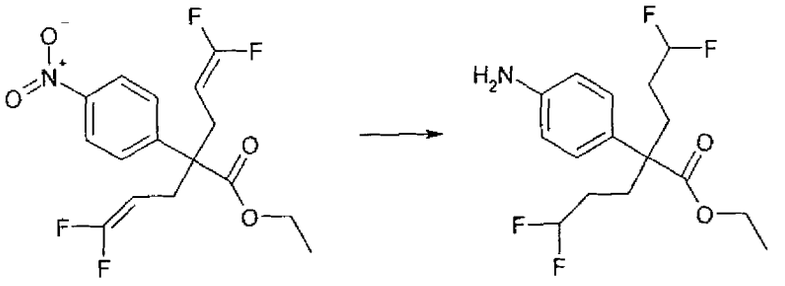
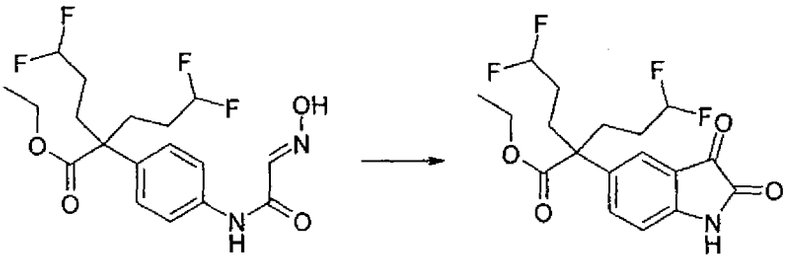


1.241 g of chloral hydrate are dissolved in 15 ml of water, 1.99 g of Na_2SO_4 are added, and the mixture is stirred at 23°C for 10 min. A solution of 7.55 g of ethyl 2-(4-aminophenyl)-2-methylpropanoate hydrochloride in 50 ml of water is added to this solution. 2.3 g of hydroxylammonium chloride in 10 ml of water are added to the resultant suspension, and the mixture is stirred at 60°C for 5 h. The mixture is subsequently allowed to cool, during which an orange oil deposits. This mixture is washed three times with 50 ml of dichloromethane each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The mixture obtained is employed in the following reaction without further purification.

Yield: 2.4 g (86%) of ethyl 2-(3,3-difluoropropyl)-5,5-difluoro-2-[4-[[(2E)-2-hydroxyiminoacetyl]amino]phenyl]pentanoate;

LC-MS retention time: 1.86 min

Step 4: Ethyl 2-(3,3-difluoropropyl)-2-(2,3-dioxoindolin-5-yl)-5,5-difluoro-pentanoate



3.0 g of ethyl 2-(3,3-difluoropropyl)-5,5-difluoro-2-[4-[[(2E)-2-hydroxyimino-acetyl]amino]phenyl]pentanoate are added in portions to 20 ml of sulfuric acid (98%) at 50°C, during which the temperature rises to 60°C. When the addition is complete, the mixture is stirred at 50°C for a further 120 min and subsequently poured into 400 ml of ice-water. The mixture is washed three times with

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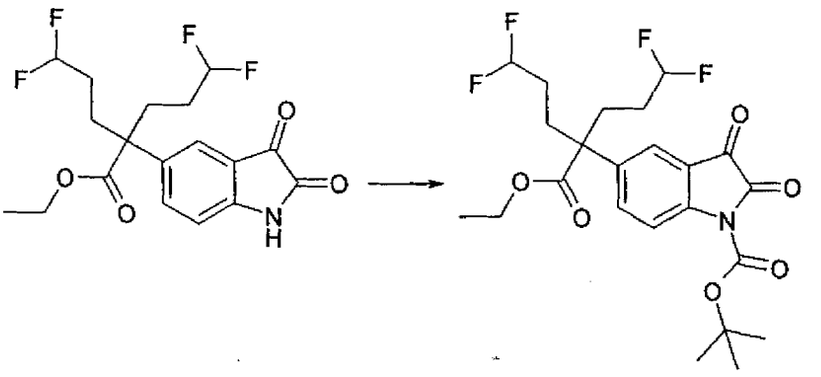
200 ml of dichloromethane/ethanol (9:1) each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The crude product obtained is employed in the next reaction without further purification. Yield: 1.9 g (66%) of ethyl 2-(3,3-difluoropropyl)-2-(2,3-dioxoindolin-5-yl)-5,5-difluoropentanoate obtained; LC-MS retention time: 2.17 min.

Step 5: 5-[1-(3,3-Difluoropropyl)-1-ethoxycarbonyl-4,4-difluorobutyl]-1-tert-butoxycarbonyl-2,3-dioxoindoline



1.119 g of di-tert-butyl dicarbonate are added to 1.9 g of ethyl 2-(3,3-difluoropropyl)-2-(2,3-dioxoindolin-5-yl)-5,5-difluoropentanoate and 50 mg of 4-dimethylaminopyridine in 50 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 12 h. The mixture is evaporated at 23°C in vacuo and processed further directly. Yield: 2.4 g (99%) of 5-[1-(3,3-difluoropropyl)-1-ethoxycarbonyl-4,4-difluorobutyl]-1-tert-butoxycarbonyl-2,3-dioxoindoline; LC-MS retention time: 2.38 min ("nonpolar" gradient).

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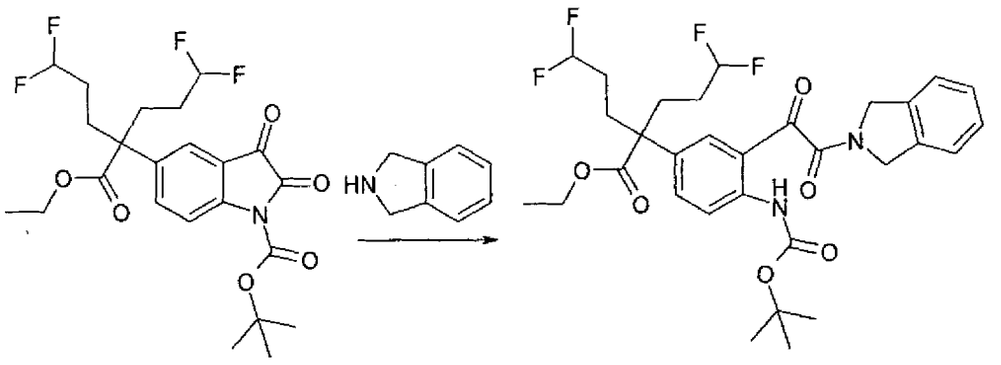
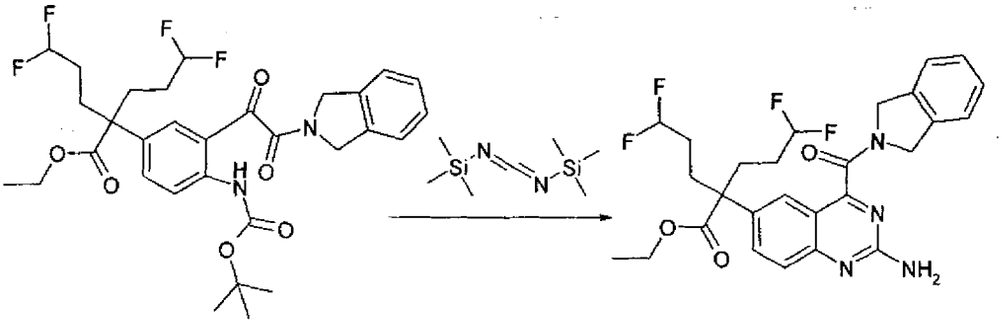
Step 6: Ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]-2-(3,3-difluoropropyl)-5,5-difluoropentanoate



584 mg of isoindoline are added to 2.4 g of 5-[1-(3,3-difluoropropyl)-1-ethoxy-carbonyl-4,4-difluorobutyl]-1-tert-butoxycarbonyl-2,3-dioxoindoline in 30 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 1 h. The mixture is evaporated to dryness in vacuo and purified by column chromatography, giving 700 mg (24%) of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxoacetyl)phenyl]- 2-(3,3-difluoropropyl)-5,5-difluoropentanoate; LC-MS retention time: 2.72 min ("nonpolar" gradient).

Step 7: Ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-5,5-difluoropentanoate



700 mg of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]-2-methylpropanoate are dissolved in 20 ml of acetonitrile under argon. 175 mg of caesium fluoride and 317 µl of bis(trimethylsilyl)carbodiimide are added to the solution. The mixture is stirred at room temperature for 15 min, and 3 ml of hydrochloric acid (1N) are then added, and the mixture is

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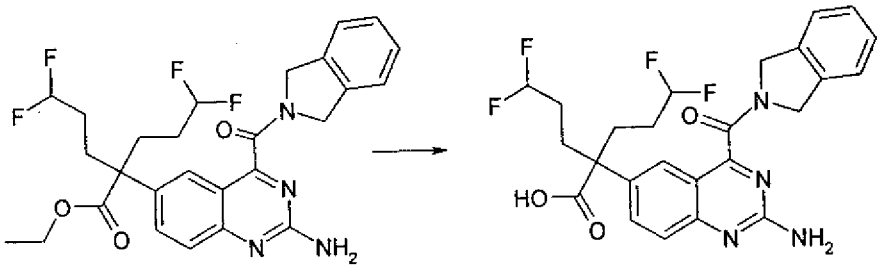
neutralised using bicarbonate. The aqueous phase is washed three times with 100 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate, filtered and evaporated to dryness in vacuo. Yield: 630 mg (100%) of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylpropanoate (oil); LC-MS retention time: 2.29 min ("nonpolar" gradient).

Step 8: 2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-5,5-difluoropentanoic acid



500 mg of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-5,5-difluoropentanoate are dissolved in 7 ml of tetrahydrofuran, and 5 ml of 2N sodium hydroxide solution are added. The mixture is stirred at 50°C for 4 h and subsequently evaporated in vacuo. The mixture is then adjusted to pH2 using 3 ml of 25% hydrochloric acid with ice-cooling, with yellow crystals precipitating. The precipitate obtained is filtered off and dried in vacuo. Yield: 170 mg (36%) of 2-[2-2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-(3,3-difluoropropyl)-5,5-difluoropentanoic acid;
LC-MS retention time: 1.58 min ("nonpolar" gradient).

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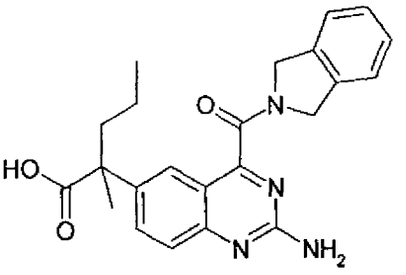
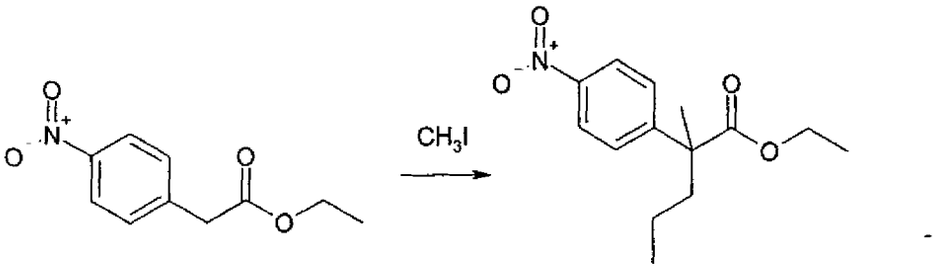
Example 14

Preparation of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl-2-methyl-pentanoic acid ("A67")



Step 1: 2-Methyl-2-(4-nitrophenyl)pentanoic acid



10 g of ethyl 4-nitrophenylacetate are dissolved in 30 ml of DMF, added dropwise to a suspension of 2.1 g of sodium hydride in 20 ml of DMF with ice-cooling and stirred for 30 min. 3 ml of methyl iodide are subsequently added, and the mixture is stirred at 23°C for 12 h. The reaction mixture is subsequently stirred into 100 ml of saturated ammonium chloride solution. The mixture is washed four times with 100 ml of ethyl acetate each time, the combined organic phases with 100 ml of sodium chloride solution, dried over sodium sulfate and, after filtration, evaporated to dryness in vacuo. The residue is purified by column chromatography (reversed phase). Yield: 6.7 g (33%) of 2-methyl-2-(4-nitrophenylpentanoic acid; LC-MS retention time: 2.33 min.

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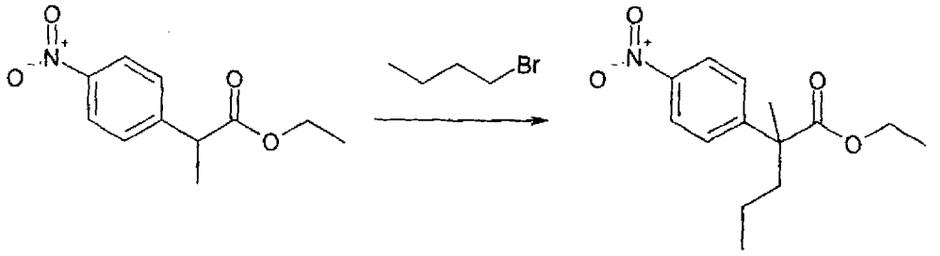
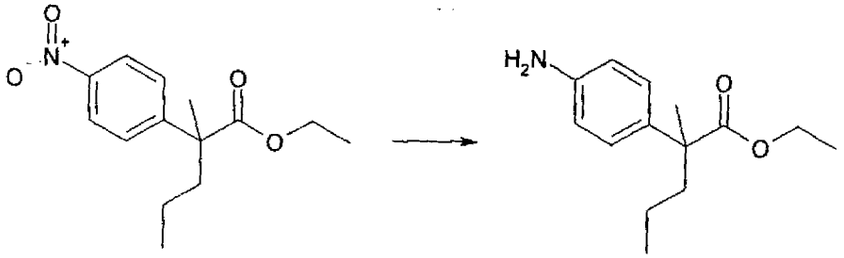
Step 2: 2-Methyl-2-(4-nitrophenyl)pentanoic acid



3.35 g of 2-methyl-2-(4-nitrophenyl)pentanoic acid are dissolved in 20 ml of DMF, added dropwise to a suspension of 720 mg of sodium hydride in 10 ml of DMF with ice-cooling and stirred for 30 min. 1.55 ml of 1-bromopropane are subsequently added, and the mixture is stirred at 23°C for 12 h. The reaction mixture is subsequently stirred into 25 ml of saturated ammonium chloride solution. The mixture is washed four times with 25 ml of ethyl acetate each time, the combined organic phases with 50 ml of sodium chloride solution, dried over sodium sulfate and, after filtration, evaporated to dryness in vacuo. The residue is purified by column chromatography (reversed phase). Yield: 2.7 g (68%) of 2-methyl-2-(4-nitrophenyl)pentanoic acid; LC-MS retention time: 2.50 min;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] 8.24 – 8.17 (m, 2H), 7.60 – 7.54 (m, 2H), 4.12 (q, J = 7.0, 2H), 2.00 – 1.87 (m, 2H), 1.53 (s, 3H), 1.19 (t, J = 7.1, 2H), 1.14 (t, J = 7.1, 3H), 0.89 (t, J = 7.3, 3H).

Step 3: Ethyl 2-(4-aminophenyl)-2-methylpentanoate



2.6 g of 2-methyl-2-(4-nitrophenyl)pentanoic acid are dissolved in 30 ml of tetrahydrofuran, 1 g of 5% Pd/C (52.3% of water) is added, and the mixture is stirred at 23°C under a hydrogen atmosphere for 1 h. After aeration, the solid material is filtered off, and the filtrate is evaporated to dryness in vacuo. Yield:

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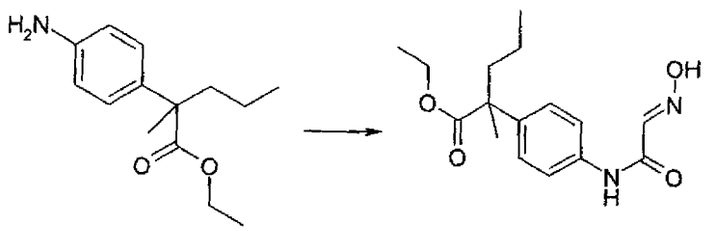
2.2 g (95%) of ethyl 2-(4-aminophenyl)-2-methylpropanoate; LC-MS retention time: 1.99 min.

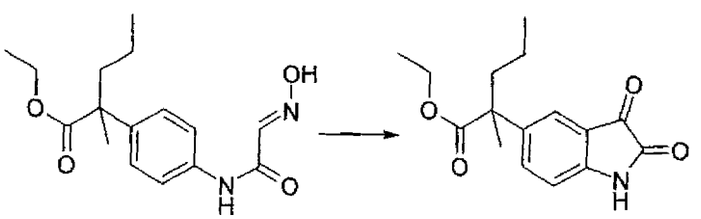
Step 4: Ethyl 2-[4-[[(2E)-2-hydroxyiminoacetyl]amino]phenyl]-2-methyl-pentanoate



1.819 g of chloral hydrate are dissolved in 20 ml of water, 2.841 g of Na_2SO_4 are added, and the mixture is stirred at 23°C for 10 min. A solution of 2.3 g of ethyl 2-(4-aminophenyl)-2-methylpentanoate hydrochloride in 20 ml of water is added to this solution. 2.1 g of hydroxylammonium chloride in 10 ml of water are added to the resultant suspension, and the mixture is stirred at 60°C for 4 h. The mixture is subsequently allowed to cool, during which an orange oil deposits. This mixture is washed three times with 50 ml of dichloromethane each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The mixture obtained is employed in the following reaction without further purification.

Yield: 2.8 g (94%) of ethyl 2-[4-[[(2E)-2-hydroxyiminoacetyl]amino]phenyl]-2-methylpentanoate; LC-MS retention time: 2.23 min.

Step 5: Ethyl 2-(2,3-dioxoindolin-5-yl)-2-methylpentanoate



2.8 g of ethyl 2-[4-[[(2E)-2-hydroxyiminoacetyl]amino]phenyl]-2-methyl-propanoate are added in portions to 15 ml of sulfuric acid (98%) at 50°C, during which the temperature rises to 60°C. When the addition is complete, the

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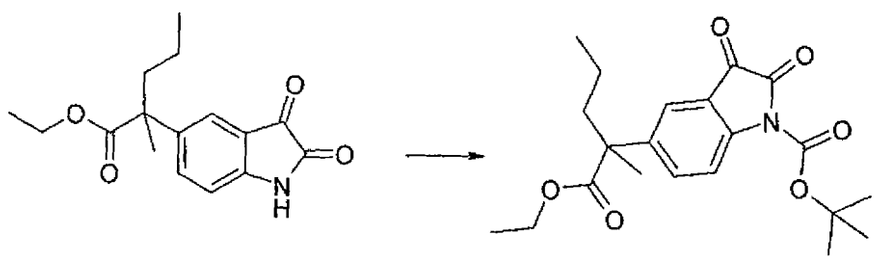
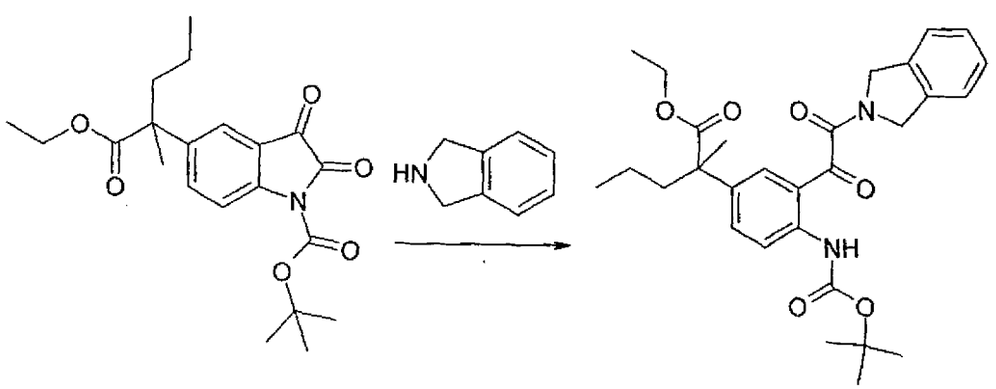
mixture is stirred at 50°C for a further 120 min and subsequently poured into 100 ml of ice-water. The mixture is washed 3 times with 50 ml of dichloromethane/ethanol (9:1) each time, the combined organic phases are dried over sodium sulfate, filtered off and evaporated to dryness in vacuo. The crude product obtained is employed in the next reaction without further purification. Yield: 1.2 g (35%) of ethyl 2-(2,3-dioxoindolin-5-yl)-2-methylpentanoate; LC-MS retention time: 2.23 min.

Step 6: 5-(2-Ethoxy-1-methylbutyl-2-oxoethyl))-1-tert-butoxycarbonyl-2,3-dioxoindoline



1.0 g of di-tert-butyl dicarbonate are added to 1.2 g of ethyl 2-(2,3-dioxoindolin-5-yl)-2-methylpentanoate and 50 mg of 4-dimethylaminopyridine in 30 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 12 h. The mixture is evaporated at 23°C in vacuo and processed further directly. Yield: 1.6 g (99%) of 5-(2-ethoxy-1-methylbutyl-2-oxoethyl))-1-tert-butoxycarbonyl-2,3-dioxoindoline; LC-MS retention time: 2.82 min.

Step 7: Ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]-2-methylpentanoate



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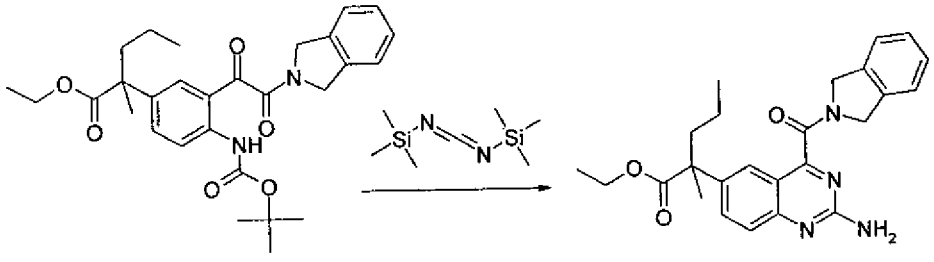
0.489 g of isoindoline are added to 1.6 g of 5-(2-ethoxy-1-methylbutyl-2-oxo-ethyl))-1-tert-butoxycarbonyl-2,3-dioxoindoline in 20 ml of tetrahydrofuran, and the mixture is subsequently stirred at 23°C for 1 h. The mixture is evaporated to dryness in vacuo and purified by column chromatography, giving 200 mg (10%) of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]-2-methylpentanoate;
LC-MS retention time: 2.98 min ("nonpolar" gradient).

Step 8: Ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl-2-methylpentanoate



200 mg of ethyl 2-[4-(tert-butoxycarbonylamino)-3-(2-isoindolin-2-yl-2-oxo-acetyl)phenyl]-2-methylpentanoate are dissolved in 10 ml of acetonitrile under argon. 61 mg of caesium fluoride and 106 µl of bis(trimethylsilyl)carbodiimide are added to the solution. The mixture is stirred at room temperature for 15 min, and 6 ml of hydrochloric acid (1N) are then added, and the mixture is neutralised using bicarbonate. The aqueous phase is washed three times with 20 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate, filtered and evaporated to dryness in vacuo. Yield: 150 mg (88%) of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methyl-pentanoate (oil); LC-MS retention time: 1.97 min ("nonpolar" gradient).

Step 9: 2-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl-2-methyl-pentanoic acid

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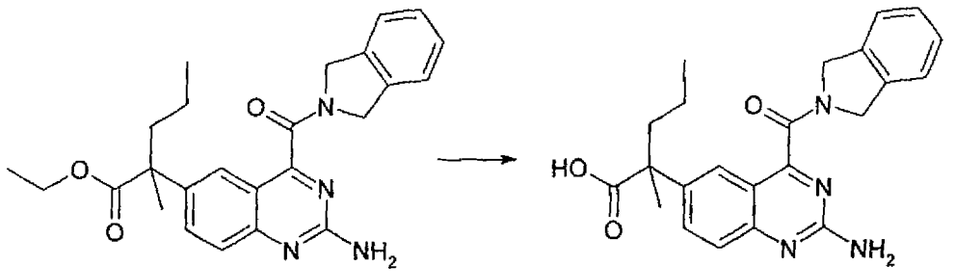
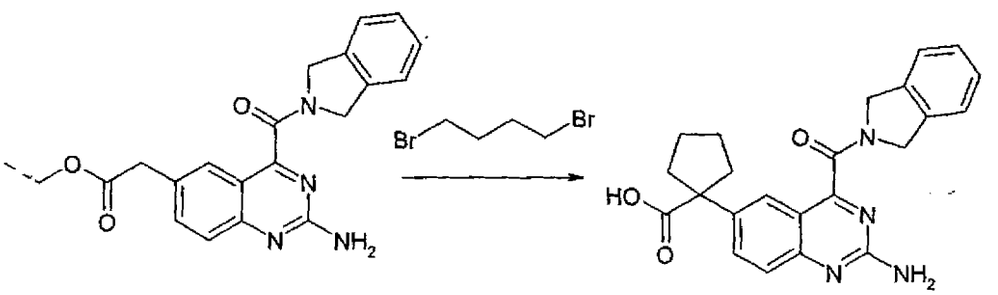


150 mg of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl-2-methylpentanoate are dissolved in 2 ml of tetrahydrofuran, and 2 ml of 2N sodium hydroxide solution are added. The mixture is stirred at 50°C for 12 h, and tetrahydrofuran is subsequently stripped off in vacuo. The mixture is diluted with 4 ml of water and then adjusted dropwise to pH2 using 25% hydrochloric acid with ice-cooling, with yellow crystals precipitating. The precipitate obtained is filtered off and dried in vacuo. Yield: 80 mg (57%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl-2-methylpentanoic acid; LC-MS retention time: 1.51 min.

Example 15

Preparation of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]cyclopentanecarboxylic acid ("A68")



188 mg of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetate are suspended in 1 ml of DMF, and 60 µl of 1,4-dibromobutane are added. 80 mg of sodium hydride are subsequently added with ice-cooling, and the mixture is stirred with cooling for a further 30 min. After 1 h at 23°C, the mixture is re-cooled, and a further 10 mg of sodium hydride are added to the mixture. The mixture is stirred at 23°C for a further 30 min, 1 ml of 2N sodium

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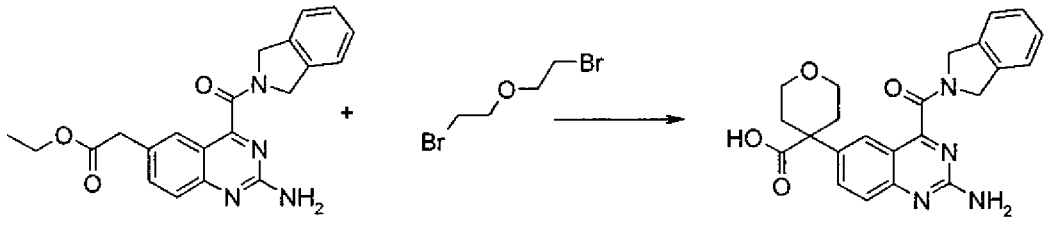
hydroxide solution is added, and the mixture is stirred at 70°C for 12 h. After cooling to 23°C, the mixture is acidified by dropwise addition of 1N hydrochloric acid, with a yellow precipitate forming. This is filtered off, washed with water and dried at 50°C for 12 h.

Yield: 83 mg (41%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-cyclopentanecarboxylic acid; LC-MS retention time: 2.13 min.

Example 16

Preparation of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]tetrahydropyran-4-carboxylic acid ("A69")



188 mg of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetate are suspended in 1 ml of DMF, and 1 ml of bis(2-bromoethyl) ether is added. 80 mg of sodium hydride are subsequently added with ice-cooling, and the mixture is stirred with cooling for a further 30 min. After 1 h at 23°C, the mixture is re-cooled, and a further 10 mg of sodium hydride are added to the mixture. The mixture is stirred at 23°C for a further 30 min, 1 ml of 2N sodium hydroxide solution is added, and the mixture is stirred at 70°C for 12 h. After cooling to 23°C, the mixture is acidified by dropwise addition of 1N hydrochloric acid, with a yellow precipitate forming. This is filtered off, washed with water and dried at 50°C for 12 h.

Yield: 50 mg (24%) of 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-tetrahydropyran-4-carboxylic acid; LC-MS retention time: 2.01 min.

Example 17

Preparation of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5-methylhexanoic acid ("A70")

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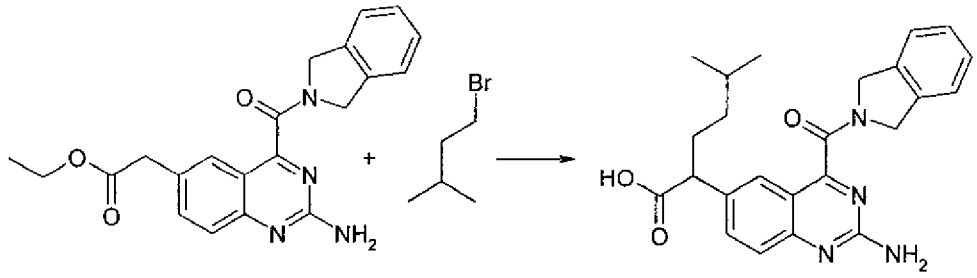
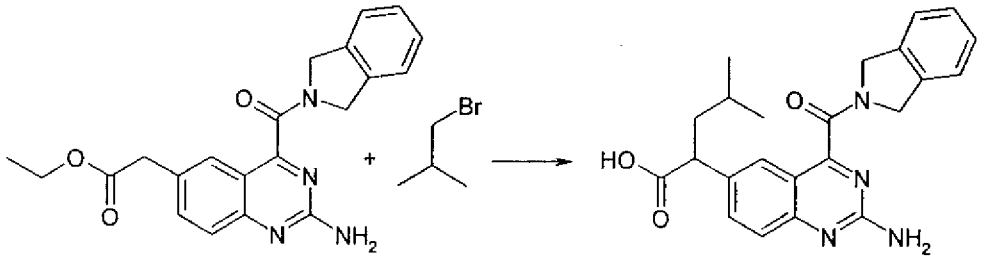


94 mg of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetate are suspended in 1 ml of DMF, and 31 µl of 1-bromo-3-methylbutane are added. 10 mg of sodium hydride are subsequently added with ice-cooling, and the mixture is stirred with cooling for a further 30 min. After 1 h at 23°C, the mixture is re-cooled, and a further 10 mg of sodium hydride are added to the mixture. The mixture is stirred at 23°C for a further 30 min, 1 ml of 2N sodium hydroxide solution is added, and the mixture is stirred at 60°C for 12 h. After cooling to 23°C, the mixture is acidified by dropwise addition of 1N hydrochloric acid, with a yellow precipitate forming. This is filtered off, washed with water and dried at 50°C for 12 h.

Yield: 48 mg (46%) of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-5-methylhexanoic acid; LC-MS retention time: 2.05 min.

Example 18

Preparation of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]4-methylpentanoic acid ("A71")



188 mg of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetate are suspended in 1 ml of DMF, and 54 µl of 1-bromo-2-methylpropane are added. 20 mg of sodium hydride are subsequently added with ice-cooling, and the mixture is stirred with cooling for a further 30 min. After 1 h at 23°C, the mixture is re-cooled, and a further 20 mg of sodium hydride are added to the

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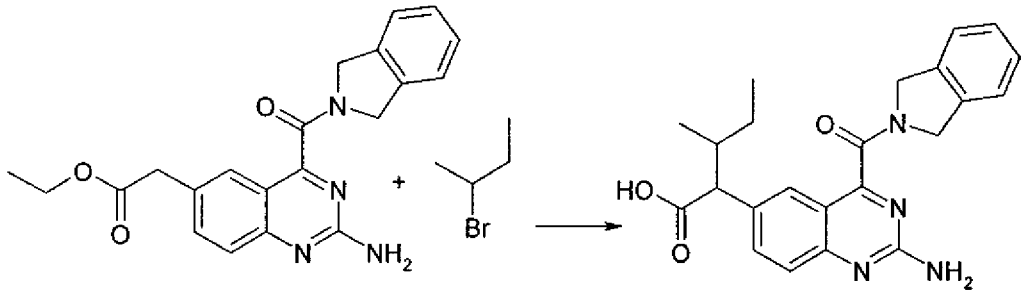
mixture. The mixture is stirred at 23°C for a further 30 min, 1 ml of 2N sodium hydroxide solution is added, and the mixture is stirred at 60°C for 12 h. After cooling to 23°C, the mixture is acidified by dropwise addition of 1N hydrochloric acid, with a yellow precipitate forming. This is filtered off, washed with water and dried at 50°C for 12 h.

Yield: 139 mg (69%) of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]4-methylpentanoic acid; LC-MS retention time: 1.93 min.

Example 19

Preparation of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-3-methylpentanoic acid ("A72")



188 mg of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetate are suspended in 1 ml of DMF, and 54 µl of 1-bromobutane are added. 20 mg of sodium hydride are subsequently added with ice-cooling, and the mixture is stirred with cooling for a further 30 min. After 1 h at 23°C, the mixture is re-cooled, and a further 20 mg of sodium hydride are added to the mixture. The mixture is stirred at 23°C for a further 30 min, 1 ml of 2N sodium hydroxide solution is added, and the mixture is stirred at 60°C for 12 h. After cooling to 23°C, the mixture is acidified by dropwise addition of 1N hydrochloric acid, with a yellow precipitate forming. This is filtered off, washed with water and dried at 50°C for 12 h.

Yield: 81 mg (40%) of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-3-methylpentanoic acid; LC-MS retention time: 1.91 min.

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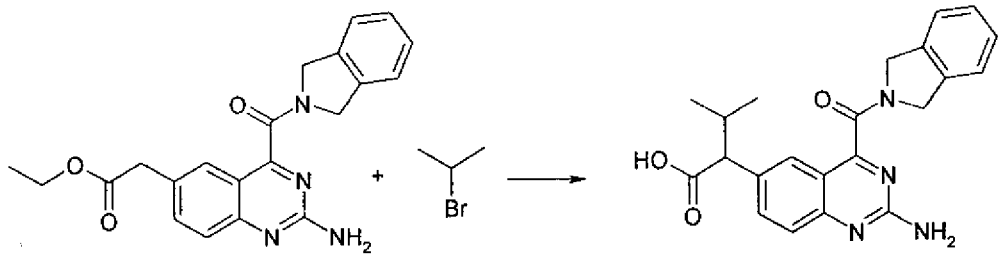
Example 20

Preparation of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-3-methyl-butanoic acid ("A73")



188 mg of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetate are suspended in 1 ml of DMF, and 54 µl of 2-bromopropane are added. 20 mg of sodium hydride are subsequently added with ice-cooling, and the mixture is stirred with cooling for a further 30 min. After 1 h at 23°C, the mixture is re-cooled, and a further 20 mg of sodium hydride are added to the mixture. The mixture is stirred at 23°C for a further 30 min, 1 ml of 2N sodium hydroxide solution is added, and the mixture is stirred at 60°C for 12 h. After cooling to 23°C, the mixture is acidified by dropwise addition of 1N hydrochloric acid, with a yellow precipitate forming. This is filtered off, washed with water and dried at 50°C for 12 h.

Yield: 78 mg (40%) of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-3-methylbutanoic acid; LC-MS retention time: 1.81 min.

Example 21

Preparation of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-carbamoylpent-4-enoic acid ("A74")

"A74" is obtained in accordance with the following scheme:

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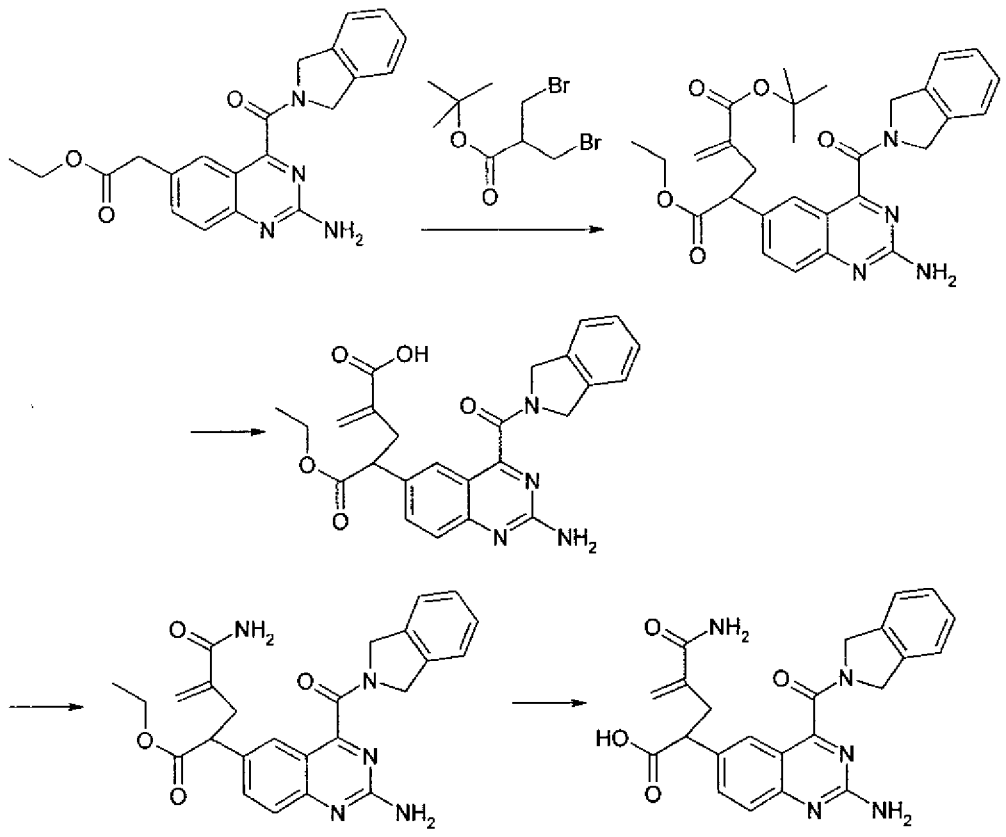
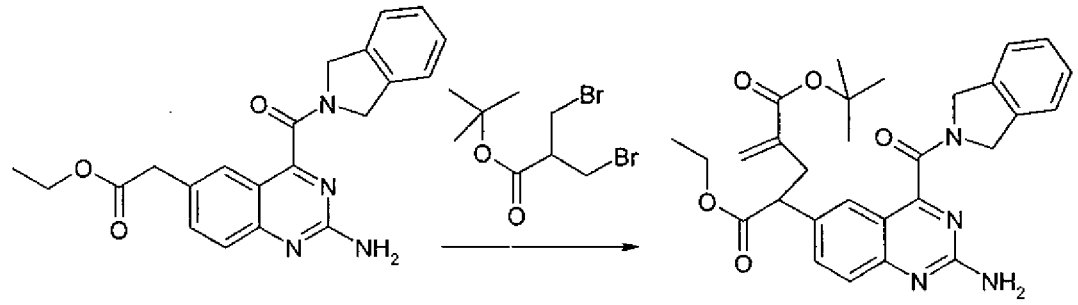


Step 1: O1-tert-Butyl O5-ethyl 4-[2-amino-4-(isoindoline-2-carbonyl)-quinazolin-6-yl]-2-methylenepentanedioate



1 g of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetate are suspended in 10 ml of DMF, and 1 g of tert-butyl 3-bromo-2-(bromomethyl)-propanoate is added. 324 mg of sodium hydride are subsequently added with ice-cooling, and the mixture is stirred with cooling for a further 30 min. After 1 h at 23°C, the mixture is poured into 50 ml of saturated ammonium chloride

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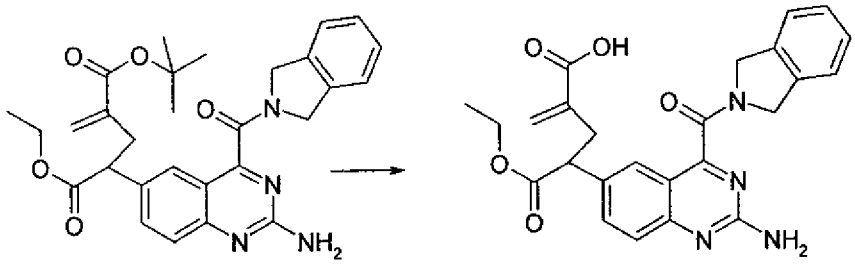
solution, with a precipitate forming. This is filtered off, washed with water and dried at 50°C for 12 h. Yield: 900 mg (66%) of O1-tert-butyl O5-ethyl 4-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylenepentanedioate; LC-MS retention time: 2.40 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1) δ [ppm] 7.97 (dd, *J* = 8.8, 1.8, 1H), 7.89 (d, *J* = 1.7, 1H), 7.72 (d, *J* = 8.8, 1H), 7.39 (d, *J* = 7.5, 1H), 7.26 (dt, *J* = 23.3, 7.1, 2H), 7.16 (d, *J* = 7.5, 1H), 5.87 (s, 1H), 5.40 (s, 1H), 5.00 (s, 2H), 4.75 (s, 2H), 3.98 (q, *J* = 7.2, 2H), 1.90 (s, 9H), 1.32 (s, 1H), 1.12 (t, *J* = 7.2, 3H).

Step 2: 4-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylene-pentanedioic acid O5-ethyl ester



200 µl of trifluoroacetic acid are added to 100 mg of O1-tert-butyl O5-ethyl 4-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylenepentanedioate in 1 ml of dichloromethane, and the mixture is stirred at 23°C for 3 h. The mixture is subsequently evaporated to dryness in vacuo and reacted further directly.

Yield: 70 mg (76%) of 4-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylenepentanedioic acid O5-ethyl ester; LC-MS retention time: 1.80 min.

Step 3: Ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-carbamoylpent-4-enoate

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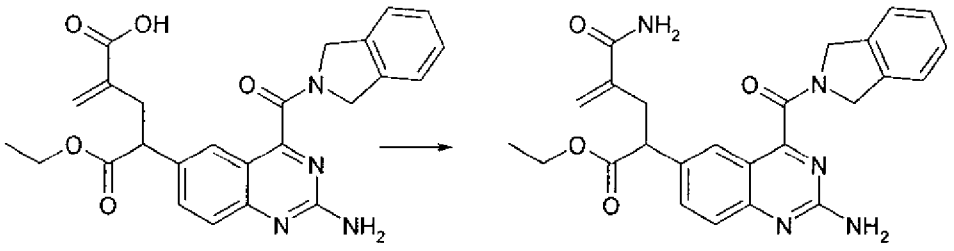
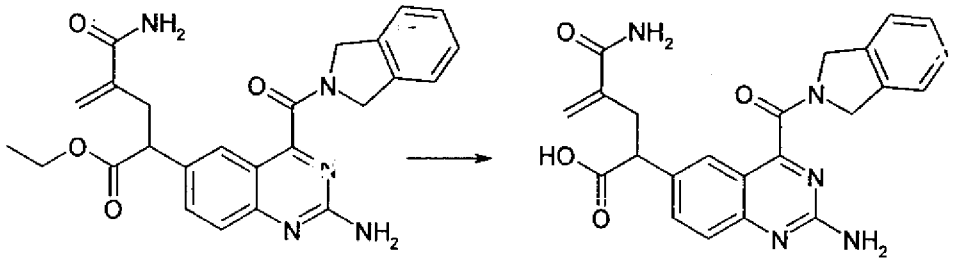


1 ml of thionyl chloride is added at 23°C to 90 mg of 4-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-2-methylenepentanedioic acid O5-ethyl ester, and the mixture is stirred for 1 h. The mixture is subsequently evaporated at 40°C in vacuo, taken up in 1 ml of tetrahydrofuran, and 1 ml of a 0.5 M ammonia solution in dioxane is added. After 30 min, the mixture is evaporated in vacuo and employed directly in the next reaction. Yield: 89 mg (99%) of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-carbamoylpent-4-enoate; LC-MS retention time: 1.66 min.

Step 4: 1-[2-Amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-carbamoyl-pent-4-enoic acid ("A74")



89 mg of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-carbamoyl-pent-4-enoic acid are dissolved 0.5 ml of tetrahydrofuran and 0.5 ml of methanol. 1 ml of 2N sodium hydroxide solution is added to this solution, and the mixture is stirred at 23°C for 2 h. The mixture is then acidified by dropwise addition of 1N hydrochloric acid, with a yellow precipitate forming. This is filtered off, washed with water and dried at 50°C for 12 h. Yield: 69 mg (83%) of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-carbamoylpent-4-enoic acid; LC-MS retention time: 1.39 min.

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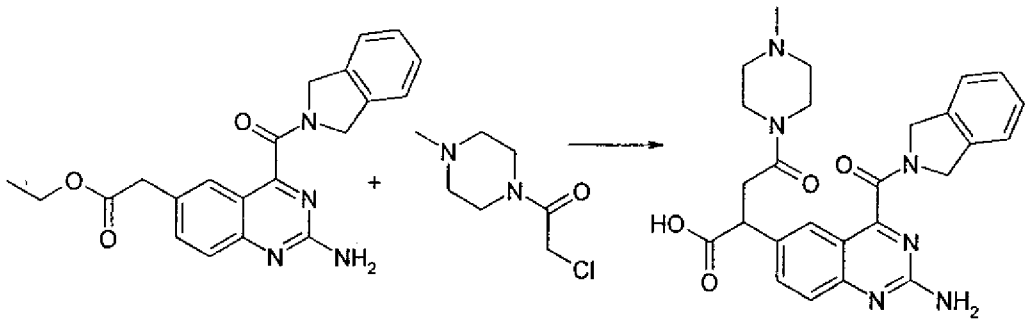
Example 22

Preparation of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-(4-methylpiperazin-1-yl)-4-oxobutanoic acid ("A75")



188 mg of ethyl 2-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]acetate are suspended in 1 ml of DMF, and 109 mg of 2-chloro-1-(4-methylpiperazin-1-yl)ethanone are added. 30 mg of sodium hydride are subsequently added with ice-cooling, and the mixture is stirred with cooling for a further 30 min. After 1 h at 23°C, the mixture is re-cooled, and a further 30 mg of sodium hydride are added to the mixture. The mixture is stirred at 23°C for a further 30 min, 1 ml of 2N sodium hydroxide solution is added, and the mixture is stirred at 60°C for 12 h. After cooling to 23°C, the mixture is acidified by dropwise addition of 1N hydrochloric acid, with a yellow precipitate forming. This is filtered off, washed with water and dried at 50°C for 12 h.

Yield: 210 mg (86%) of 1-[2-amino-4-(isoindoline-2-carbonyl)quinazolin-6-yl]-4-(4-methylpiperazin-1-yl)-4-oxobutanoic acid; LC-MS retention time: 1.05 min.

Example 23

Preparation of [2-amino-6-[(4-methylpiperazin-1-yl)methyl]quinazolin-4-yl]-isoindolin-2-ylmethanone ("A76")

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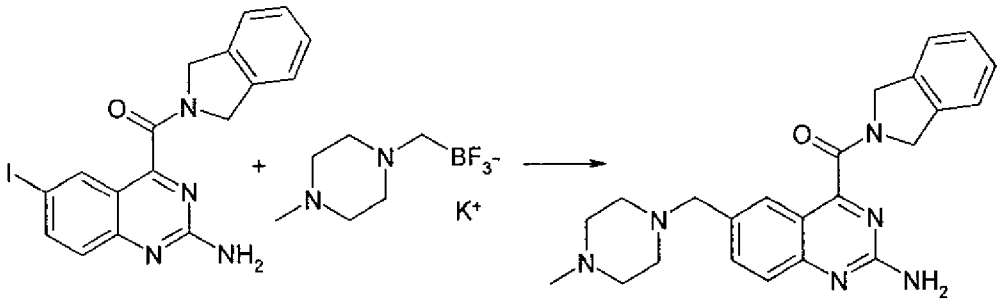

75 mg of (2-amino-6-iodoquinazolin-4-yl)isoindolin-2-ylmethanone are suspended in 2 ml of tetrahydrofuran and 7 µl of water together with 40 mg of potassium 1-methyl-4-trifluoroboratomethylpiperazine, 1 mg of palladium diacetate, 4 mg of ((2,4,6 triisopropyl)phenyl)dicyclohexylphosphine and 176 mg of caesium carbonate, and the mixture is stirred at 80°C for 48 h. After cooling, the mixture is filtered through kieselguhr, rinsed three times with 5 ml of tetrahydrofuran each time, and the filtrate is evaporated to dryness in vacuo. The residue is purified by means of preparative HPLC, and the title compound is isolated.

Yield: 42 mg (53%) of [2-amino-6-[(4-methylpiperazin-1-yl)methyl]quinazolin-4-yl]isoindolin-2-ylmethanone; LC-MS retention time: 1.14 min;

^{1}H NMR (500 MHz, DMSO-d_6/TFA-d_1) δ [ppm] 8.33 (d, J = 1.7, 1H), 8.23 (dd, J = 8.7, 1.7, 1H), 7.83 (d, J = 8.6, 1H), 7.45 (d, J = 7.5, 1H), 7.31 (dt, J = 21.5, 7.2, 2H), 7.22 (d, J = 7.5, 1H), 5.03 (s, 2H), 4.81 (s, 2H), 4.59 (s, 2H), 3.75 – 3.26 (m, 8H), 2.84 (s, 3H).

The following compounds are obtained analogously to the preparation of the above-mentioned examples:

N-dimethyl-2-amino-6-(1-ethylcarbamoylcyclobutyl)quinazoline-4-carboxamide ("A77")

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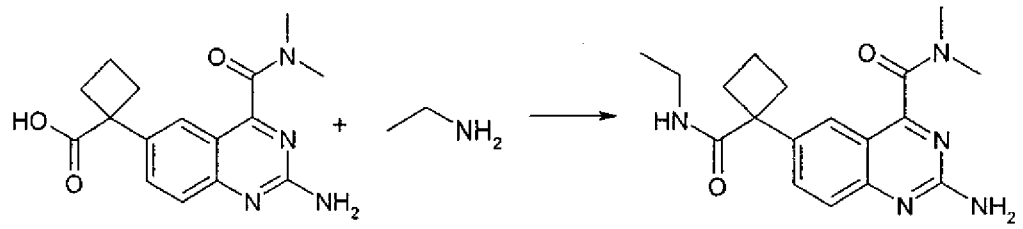
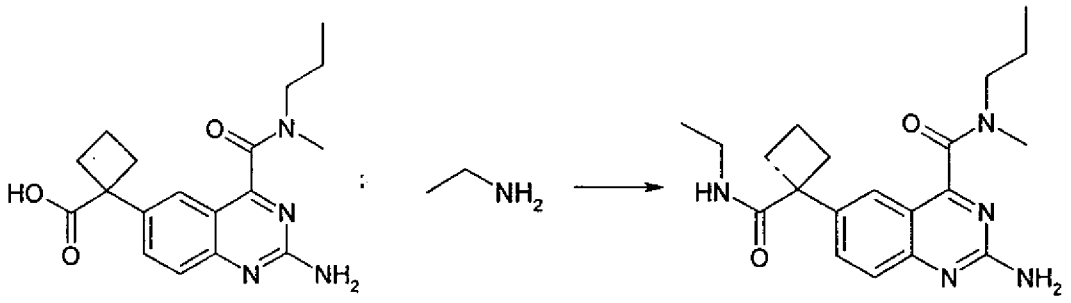


Yield: 20 mg (15%) LC-MS retention time: 1.24 min;
^{1}H NMR (400 MHz, DMSO-d_6/TFA-d_1) δ [ppm] 8.05 (dd, *J* = 8.8, 1.9, 1H), 7.75 (d, *J* = 8.7, 1H), 7.69 (d, *J* = 1.8, 1H), 3.19 (s, 3H), 3.08 (q, *J* = 7.2, 2H), 2.96 (s, 3H), 2.85 – 2.77 (m, 2H), 2.41 (dt, *J* = 11.9, 8.8, 2H), 1.96 – 1.74 (m, 2H), 0.98 (t, *J* = 7.2, 3H).

N-Methylpropyl-2-amino-6-(1-ethylcarbamoylcyclobutyl)quinazoline-4-carboxamide ("A78")



Yield: 135 mg (43%) LC-MS retention time: 1.48 min;
^{1}H NMR (400 MHz, DMSO-d_6/TFA-d_1) δ [ppm] 8.06 (dd, *J* = 8.7, 2.0, 1H), 7.75 (dd, *J* = 8.7, 2.7, 1H), 7.68 (dd, *J* = 8.4, 1.9, 1H), 3.64 – 3.18 (m, 2H), 3.16 (s, 2H), 3.09 (qd, *J* = 7.2, 4.7, 2H), 2.93 (s, 2H), 2.80 (ddd, *J* = 11.6, 8.8, 4.3, 2H), 2.39 (ddd, *J* = 11.9, 9.2, 4.6, 2H), 1.84 – 1.70 (m, 2H), 1.98 – 1.50 (m, 2H), 0.98 (t, *J* = 7.2, 3H), 1.07 – 0.69 (m, 2H).

N-Diethyl-2-amino-6-(1-ethylcarbamoylcyclobutyl)quinazoline-4-carboxamide ("A79")

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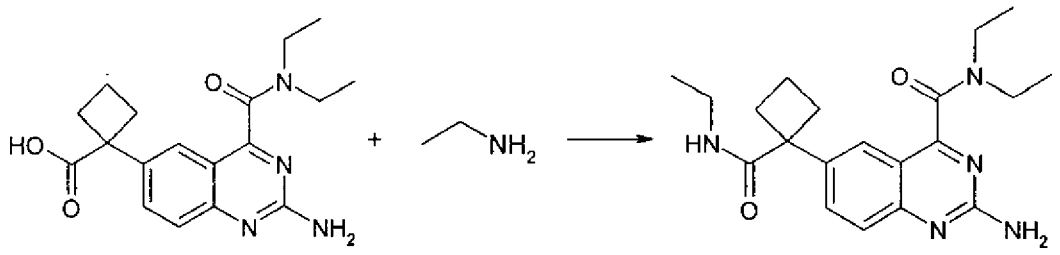
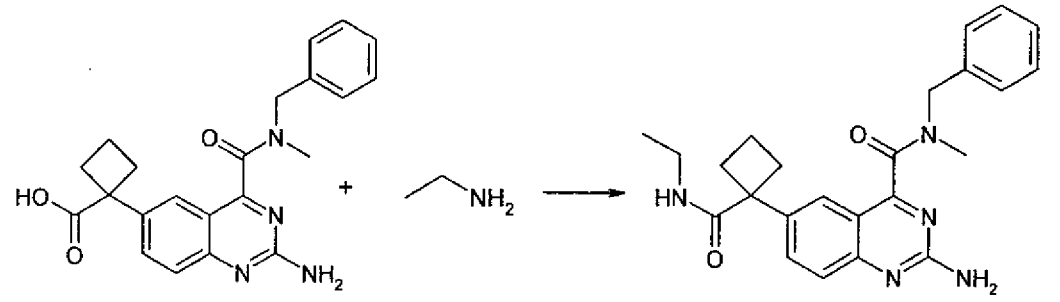


Yield: 51 mg (30%) LC-MS retention time: 1.48 min;
^{1}H NMR (400 MHz, DMSO-d_6/TFA-d_1) δ [ppm] 8.07 (dd, J = 8.7, 2.0, 1H), 7.75 (d, J = 8.8, 1H), 7.65 (d, J = 1.9, 1H), 3.64 (q, J = 7.0, 2H), 3.28 (q, J = 7.0, 2H), 3.08 (q, J = 7.2, 2H), 2.80 (ddd, J = 12.0, 8.8, 6.2, 2H), 2.37 (dt, J = 12.0, 8.9, 2H), 1.96 – 1.73 (m, 2H), 1.30 (t, J = 7.1, 3H), 1.08 (t, J = 7.0, 3H), 0.98 (t, J = 7.2, 3H).

N-Benzylmethyl-2-amino-6-(1-ethylcarbamoylcyclobutyl)quinazoline-4-carboxamide ("A80")



Yield: 48 mg (23%) LC-MS retention time: 1.72 min;
^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]– 7.20 (m, 8H), 6.96 (s, 2H), 4.86 – 4.29 (m, 2H), 3.28 (s, 3H), 3.08 – 2.99 (m, 2H), 2.72 – 2.63 (m, 2H), 2.38 – 2.19 (m, 2H), 1.92 – 1.64 (m, 2H), 1.00 – 0.84 (m, 3H).

Ethyl 1-[4-(*tert*-butoxycarbonylamino)-3-(dimethylaminooxalyl)phenyl]cyclobutanecarboxylate ("A81")

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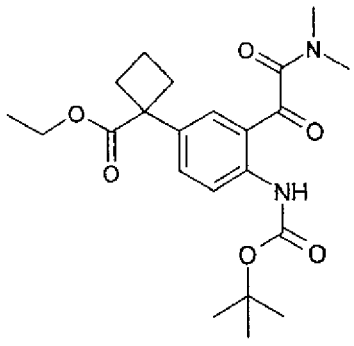
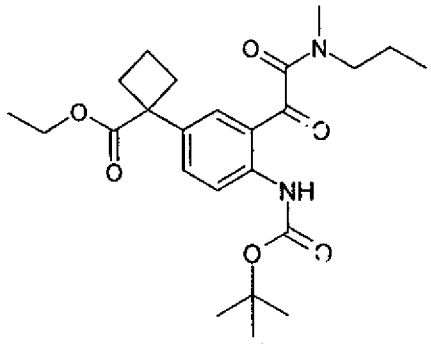


Yield: 306 mg (49%)

LC-MS retention time: 2.46 min ("nonpolar" gradient);

^{1}H-NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] d, J = 8.8, 1H), 7.67 (dd, J = 8.8, 2.2, 1H), 7.43 (d, J = 2.4, 1H), 4.08 (q, J = 7.1, 2H), 3.05 (s, 3H), 2.93 (s, 3H), 2.76 (ddd, J = 12.1, 9.1, 5.7, 2H), 2.45 – 2.36 (m, 2H), 2.06 – 1.79 (m, 3H), 1.52 (s, 9H), 1.14 (t, J = 7.2, 3H).

Ethyl 1-[4-(*tert*-butoxycarbonylamino)-3-(methylpropylaminooxalyl)phenyl]-cyclobutanecarboxylate ("A82")



Yield: 260 mg (39%)

LC-MS retention time: 2.69 min ("nonpolar" gradient);

^{1}H-NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.42 (dd, J = 8.9, 1.7, 1H), 7.65 (td, J = 9.0, 2.2, 1H), 7.47 (dd, J = 18.8, 2.3, 1H), 4.07 (q, J = 7.2, 2H), 3.49 – 3.14 (m, 2H), 3.02 – 2.89 (m, 3H), 2.79 – 2.70 (m, 2H), 2.46 – 2.34 (m, 2H), 2.05 – 1.74 (m, 2H), 1.72 – 1.53 (m, 2H), 1.52 (s, 9H), 1.13 (td, J = 7.1, 2.8, 3H), 0.99 – 0.74 (m, 3H).

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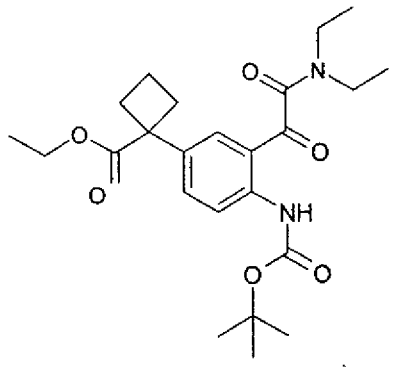
Ethyl 1-[4-(*tert*-butoxycarbonylamino)-3-(diethylaminooxalyl)phenyl]-cyclobutanecarboxylate ("A83")

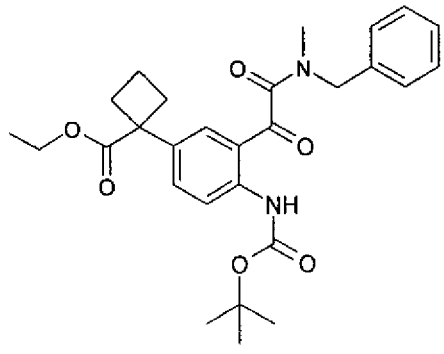


Yield: 255 mg (45%)

LC-MS retention time: 2.68 min ("nonpolar" gradient);

^{1}H-NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.43 (d, J = 9.0, 1H), 7.65 (dd, J = 8.9, 2.3, 1H), 7.47 (d, J = 2.2, 1H), 4.09 – 4.04 (m, 2H), 3.50 (q, J = 7.1, 2H), 3.24 (q, J = 7.1, 2H), 2.75 (ddd, J = 12.1, 8.9, 5.3, 2H), 2.39 (dt, J = 12.1, 9.1, 2H), 2.04 – 1.80 (m, 2H), 1.52 (s, 9H), 1.23 (t, J = 7.1, 3H), 1.13 (t, J = 7.1, 3H), 1.09 (t, J = 7.0, 3H).

Ethyl 1-[4-(*tert*-butoxycarbonylamino)-3-(benzylmethylaminooxalyl)phenyl]-cyclobutanecarboxylate ("A84")



Yield: 322 mg (43%)

LC-MS retention time: 2.84 min ("nonpolar" gradient);

^{1}H-NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.40 (d, J = 8.8, 1H), 7.65 (ddd, J = 15.8, 8.8, 2.3, 1H), 7.50 (dd, J = 24.4, 2.2, 1H), 7.45 – 7.22 (m, 5H), 4.73 – 4.49 (m, 2H), 4.12 – 3.99 (m, 2H), 2.95 – 2.87 (m, 3H), 2.74 (dddd, J =

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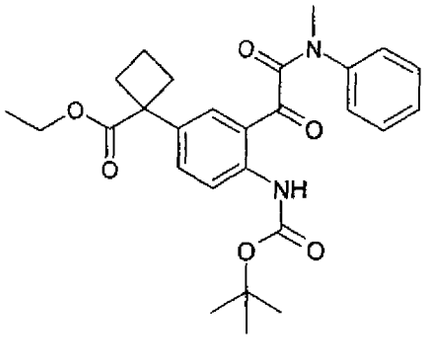
24.4, 11.9, 8.8, 5.3, 2H), 2.43 – 2.27 (m, 2H), 2.04 – 1.74 (m, 2H), 1.52 – 1.49 (m, 9H), 1.17 – 1.05 (m, 3H).

Ethyl 1-[4-(*tert*-butoxycarbonylamino)-3-(methylphenylaminooxalyl)phenyl]-cyclobutanecarboxylate ("A85")

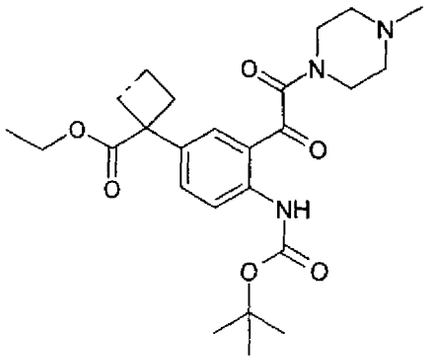


Yield: 311 mg (43%)

LC-MS retention time: 2.74 min ("nonpolar" gradient);

^{1}H-NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm]8.24 (d, J = 8.8, 1H), 7.66 – 7.51 (m, 2H), 7.34 – 7.24 (m, 3H), 7.22 – 7.17 (m, 2H), 4.11 (q, J = 7.2, 2H), 3.43 (s, 3H), 2.79 (ddd, J = 12.1, 8.9, 5.6, 2H), 2.43 (dt, J = 12.1, 9.1, 2H), 2.06 – 1.81 (m, 2H), 1.46 (s, 9H), 1.16 (t, J = 7.2, 3H).

Ethyl 1-[4-(*tert*-butoxycarbonylamino)-3-(4-methylpiperazin-1-yl)-2-oxo-acetyl]phenyl]cyclobutanecarboxylate ("A86")



Yield: 296 mg (42%)

LC-MS retention time: 1.42 min ("nonpolar" gradient);

^{1}H-NMR (500 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 8.35 (d, J = 8.8, 1H), 7.70 (dd, J = 8.8, 2.2, 1H), 7.49 (d, J = 2.4, 1H), 4.59 (d, J = 13.6, 1H), 4.13 – 4.06 (m,

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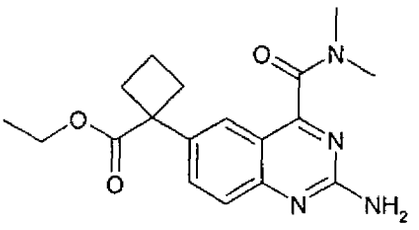
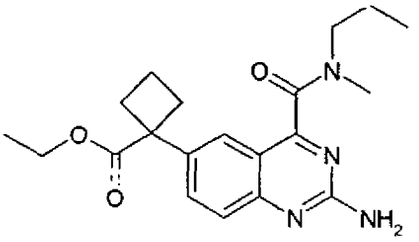
2H), 3.92 (d, J = 13.6, 1H), 3.70 – 3.58 (m, 2H), 3.47 (t, J = 13.2, 1H), 3.27 (d, J = 12.3, 1H), 3.15 (d, J = 11.4, 1H), 3.00 (s, 1H), 2.92 (s, 3H), 2.82 – 2.72 (m, 2H), 2.44 (d, J = 8.6, 2H), 2.08 – 1.74 (m, 2H), 1.52 (s, 9H), 1.16 (t, J = 7.1, 3H).

Ethyl 1-(2-amino-4-dimethylcarbamoylquinazolin-6-yl)cyclobutanecarboxylate ("A87")



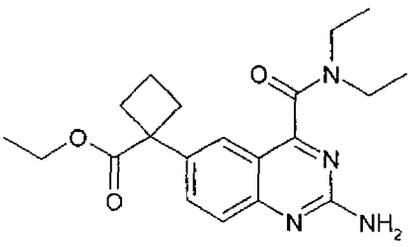
Yield: 280 mg (100%)
LC-MS retention time: 1.67 min;

Ethyl 1-(2-amino-4-(-methylpropylcarbamoyl)quinazolin-6-yl)cyclobutanecarboxylate ("A88")



Yield: 240 mg (100%)
LC-MS retention time: 1.88 min;

Ethyl 1-(2-amino-4-diethylcarbamoylquinazolin-6-yl)cyclobutanecarboxylate ("A89")



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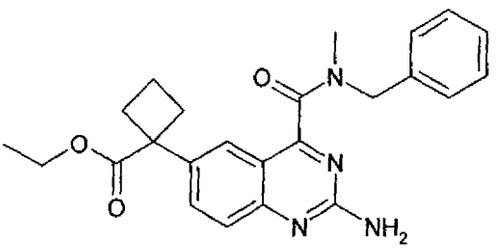
Yield: 280 mg (100%)

LC-MS retention time: 1.89 min;

Ethyl 1-(2-amino-4-(benzylmethylcarbamoyl)quinazolin-6-yl)cyclobutane-carboxylate ("A90")

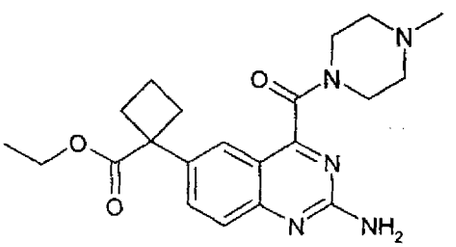


Yield: 305 mg (100%)

LC-MS retention time: 2.09 min;

^{1}H-NMR (400 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.97 (dt, J = 8.9, 2.2, 1H), 7.77 (dd, J = 8.7, 5.6, 1H), 7.63 (dd, J = 25.6, 1.8, 1H), 7.51 – 7.24 (m, 5H), 4.12 – 3.99 (m, 2H), 3.63 – 3.20 (m, 2H), 3.16 – 2.92 (m, 4H), 2.88 – 2.72 (m, 2H), 2.49 – 2.39 (m, 2H), 2.14 – 1.79 (m, 3H), 1.76 – 1.55 (m, 2H), 1.17 – 1.05 (m, 3H).

Ethyl 1-(2-amino-4-(4-methylpiperazine-1-carbonyl)quinazolin-6-yl)cyclo-butanecarboxylate ("A91")



Yield: 250 mg (100%)

LC-MS retention time: 1.33 min.

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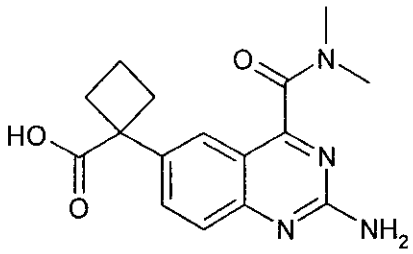
1-(2-Amino-4-dimethylcarbamoylquinazolin-6-yl)cyclobutanecarboxylic acid ("A92")

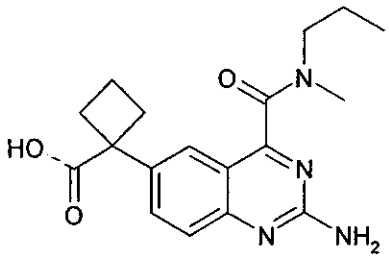


Yield: 120 mg (26%)

LC-MS retention time: 1.32 min;

^{1}H-NMR (400 MHz, DMSO-d_6/TFA-d_1): δ [ppm]8.00 – 7.96 (m, 1H), 7.79 – 7.76 (m, 1H), 7.62 – 7.58 (m, 1H), 3.19 – 2.96 (m, 6H), 2.88 – 2.71 (m, 2H), 2.52 – 2.37 (m, 2H), 2.13 – 1.77 (m, 2H).

1-(2-Amino-4-(-methylpropylcarbamoyl)quinazolin-6-yl)cyclobutanecarboxylic acid ("A93")



Yield: 125 mg (56%).

LC-MS retention time: 1.52 min;

^{1}H-NMR (400 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.99 – 7.95 (m, 1H), 7.79 – 7.74 (m, 1H), 7.60 – 7.57 (m, 1H), 3.63 – 3.20 (m, 2H), 3.16 – 2.92 (m, 4H), 2.88 – 2.72 (m, 2H), 2.49 – 2.39 (m, 2H), 2.14 – 1.79 (m, 3H), 1.76 – 1.55 (m, 2H), 1.06 – 0.71 (m, 3H).

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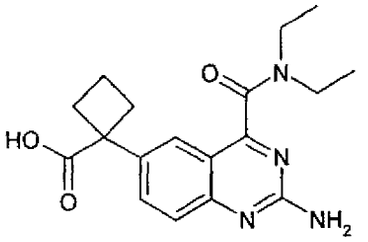
1-(2-Amino-4-diethylcarbamoylquinazolin-6-yl)cyclobutanecarboxylic acid ("A94")

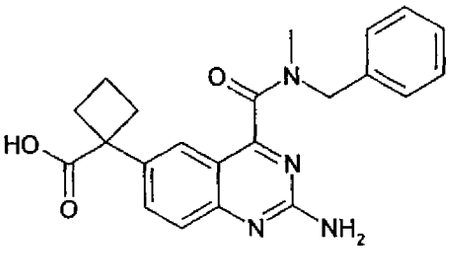


Yield: 157 mg (61%)

LC-MS retention time: 1.49 min;

^{1}H-NMR (400 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.97 (dd, J = 8.8, 1.9, 1H), 7.76 (d, J = 8.8, 1H), 7.62 (d, J = 1.9, 1H), 3.64 (q, J = 7.0, 2H), 3.29 (q, J = 6.8, 2H), 2.91 – 2.73 (m, 2H), 2.46 (dd, J = 20.0, 8.9, 2H), 2.17 – 1.79 (m, 2H), 1.31 (t, J = 7.0, 3H), 1.11 (t, J = 7.0, 3H).

1-(2-Amino-4-(benzylmethylcarbamoyl)quinazolin-6-yl)cyclobutanecarboxylic acid ("A95")



Yield: 194 mg (68%)

LC-MS retention time: 1.71 min;

^{1}H-NMR (400 MHz, DMSO-d_6/TFA-d_1): δ [ppm] 7.99 – 7.94 (m, 1H), 7.80 – 7.74 (m, 1H), 7.68 – 7.57 (m, 1H), 7.53 – 7.24 (m, 5H), 4.86 – 4.56 (m, 2H), 3.09 – 2.92 (m, 3H), 2.91 – 2.76 (m, 2H), 2.52 – 2.34 (m, 2H), 2.16 – 1.76 (m, 2H).

The following examples relate to pharmaceutical compositions:

Example A: Injection vials

A solution of 100 g of an active ingredient according to the invention and

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5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of active ingredient.

Example B: Suppositories

A mixture of 20 g of an active ingredient according to the invention with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example C: Solution

A solution is prepared from 1 g of an active ingredient according to the invention, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active ingredient according to the invention are mixed with 99.5 g of Vaseline under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active ingredient, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of active ingredient.

Example F: Dragees

Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

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Example G: Capsules

2 kg of active ingredient are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of the active ingredient.

Example H: Ampoules

A solution of 1 kg of an active ingredient according to the invention in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.