(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 June 2007 (14.06.2007)

PCT

(10) International Publication Number
WO 2007/065663 A1

(51) International Patent Classification:
A61K 31/517 (2006.01) *C07D 498/04* (2006.01)
C07D 471/04 (2006.01) *A61P 25/04* (2006.01)
C07D 487/04 (2006.01)

(21) International Application Number:
PCT/EP2006/011721

(22) International Filing Date:
6 December 2006 (06.12.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0525069.1 8 December 2005 (08.12.2005) GB

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DZIADULEWICZ, Edward, Karol** [GB/GB]; Novartis Pharmaceuticals UK Limited, Patents and Trademarks, Wimblehurst Road, Horsham, West Sussex RH12 5AB (GB). **BRAIN, Christopher, Thomas** [GB/GB]; Novartis Pharmaceuticals UK Limited, Patents and Trademarks, Wimblehurst Road, Horsham, West Sussex RH12 5AB (GB). **RITCHIE, Timothy, John** [GB/GB]; Novartis Pharmaceuticals UK Limited, Patents and Trademarks, Wimblehurst Road, Horsham, West Sussex RH12 5AB (GB). **CULSHAW, Andrew, James** [GB/GB]; Novartis Pharmaceuticals UK Limited, Patents and Trademarks, Wimblehurst Road, Horsham, West Sussex RH12 5AB (GB).

(74) Agents: **ROTH, Peter, R.** et al.; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

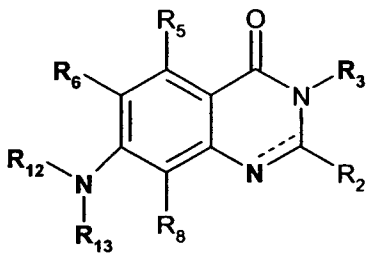
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: QUINAZOLINONE DERIVATIVES AS VANILLOID ANTAGONISTS



(I)

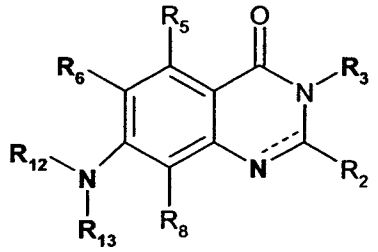
(57) Abstract: The invention relates to quinazolinone compounds of the formula (I) wherein the R groups are defined in the specification, processes for their preparation and their use as pharmaceuticals, particularly in the treatment of disorders ameliorated by administration of TRPV1 antagonists.

WO 2007/065663 A1

QUINAZOLINONE DERIVATIVES AS VANILLOID ANTAGONISTS

The present invention relates to quinazolinone derivatives as vanilloid antagonists, to processes for preparing them, to their use as pharmaceuticals and to pharmaceutical compositions containing them.

In a first aspect, the present invention provides a quinazolinone compound of the formula



(I)

,

wherein

---- is a single bond or a double bond;

R_2 is selected from

(a) C_1-C_8alkyl, C_3-C_6cycloalkyl, (C_1-C_6alkyl)amino or di-(C_1-C_6alkyl)amino;

or

(b) NH_2, hydroxyC_1-C_6alkylamino-, aminoC_1-C_6alkylamino, C_2-C_6alkenyl, di(trifluoromethyl)C_1-C_6alkyl, R_9-O-(C_1–C_6alkyl)- in which the alkyl chain is optionally substituted by trifluoromethyl, (NC)-C_1–C_6alkyl-, ($R_{10}R_{11}$N-)C_1–C_6alkyl-, (C_1–C_6alkyl)-SO_2-(C_1–C_6alkyl)-, wherein R_9, R_{10} and R_{11} are each independently H or C_1-C_6 alkyl; phenyl optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1–C_6alkyl, halogen-substituted C_1–C_6alkyl, hydroxy C_1–C_6alkyl, cyano or a group –(C=O)-R_{2a}, where R_{2a} is C_1–C_6alkyl; or 5, 6, or 7-membered, saturated or unsaturated, heterocyclic ring, directly attached to the quinazolinone ring or attached through -C_1–C_6 alkyl-, containing one, two, or three heteroatoms selected from N, O and S, and optionally substituted with one, two or three substitutents selected from C_1–C_6alkyl, C_1–C_6alkoxy, hydroxy, cyano, halo, $R_{10}R_{11}$N-, R_9-O-(C=O)-, -(C=O)-N-$R_{10}R_{11}$, =O and phenyl ;

R_3 is selected from

(a'):

phenyl substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_6alkyl, halogen-substituted C_1-C_6alkyl, hydroxyC_1-C_6alkyl, cyano or a group –C(=O)-R_{3a}, where R_{3a} is C_1-C_6alkyl; or

(b'):

C_1–C_6alkyl, (NC)-C_1–C_6alkyl-, R_9-O-(C_1–C_6alkyl)-, R_9-O-(C_1–C_6alkyl)-O-(C_1–C_6alkyl)-,$R_{10}R_{11}$N-(C_1–C_6alkyl)-, $R_{10}R_{11}$N-(C=O)-(C_1–C_6alkyl)-, or (C_1–C_6alkyl)-SO_2-(C_1–C_6alkyl)-, wherein R_9, R_{10} and R_{11} are each independently H or C_1-C_6 alkyl; or

unsubstituted phenyl, phenyl substituted with one or two substituents selected from -(C_1–C_6alkoxy)-, $R_{10}R_{11}$N-, $R_{10}R_{11}$N-(C_1–C_6alkyl)-, -SO_2-(C_1–C_6alkyl), R_9-O-(C=O)-, wherein R_9, R_{10} and R_{11} are as defined above, or with halo-substituted phenyl or a 5- or 6-membered saturated or unsaturated heterocyclic ring having one, two or three heteroatoms selected from N, O and S and optionally including a further substituent selected from halo, or phenyl substituted with three or four substituents selected from halo, hydroxyl, and C_1–C_6alkyl; or

a cycloalkyl ring having 3, 4, 5 or 6 carbon atoms, directly attached to the quinazolinone ring or attached through -C_1–C_6alkyl-, and which is optionally substituted with one or two substituents selected from C_1–C_6alkyl, C_1–C_6alkoxy, hydroxy, cyano, halo, $R_{10}R_{11}$N-, R_9-O-(C=O)-, -(C=O)-N-$R_{10}R_{11}$, and phenyl; or

benzyl, or phenyl(C_1–C_6alkyl)-, phenoxy-(C_1–C_6alkyl)- or phenyl(C=O)-(C_1–C_6alkyl)-, optionally substituted with one, two, or three substituents selected from C_1–C_6alkyl, C_1–C_6alkoxy, hydroxy, cyano, halo, $R_{10}R_{11}$N-, R_9-O-(C=O)-, -(C=O)-N-$R_{10}R_{11}$, and phenyl; or

a 5, 6, or 7- membered, saturated or unsaturated, heterocyclic ring, directly attached to the quinazolinone ring or attached through -C_1–C_6 alkyl-, containing one, two, or three heteroatoms selected from N, O and S, and optionally substituted with one, two or three substitutents selected from C_1–

C_6alkyl, C_1–C_6alkoxy, hydroxy, cyano, halo, $R_{10}R_{11}N$-, R_9-O-(C=O)-, -(C=O)-N-$R_{10}R_{11}$, =O and phenyl; or

a 9- or 10- membered aromatic or heterocyclic fused ring, directly attached to the quinazolinone ring or attached through -C_1–C_6 alkyl-, containing zero, one, two or three heteroatoms selected from N, O and S, and optionally substituted with one, two, three or four substitutents selected from C_1–C_6alkyl, C_1–C_6alkoxy, hydroxy, cyano, halo, $R_{10}R_{11}N$-, R_9-O-(C=O)-, -(C=O)-N-$R_{10}R_{11}$, and phenyl; and

R_5 and R_6 are each independently hydrogen, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, hydroxy, hydroxy-substituted C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, cyano, -C(=O)H, phenyl, (C_3-C_6cycloalkyl)C_1-C_6alkyl, (C_3-C_6cycloalkyl)C_1-C_6alkoxy, (C_1-C_6alkoxycarbonylamino)C_1-C_6alkoxy or (C_1-C_6alkylcarbonylamino)C_1-C_6alkoxy, (amino) C_1-C_6alkoxy, (dimethylamino)C_1-C_6alkoxy, or (C_1-C_6alkoxycarbonyl) C_1-C_6alkoxy;

R12 is hydrogen, formyl, C_1-C_6alkylcarbonyl or benzyl, the phenyl group of which is optionally substituted by 1, 2 or 3 substituents, selected from the group consisting of halogen, C_1-C_6alkyl, halo-C_1-C_6alkyl, hydroxy, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, halo-C_1-C_6alkoxy, C_1-C_6alkylthio, halo-C_1-C_6alkylthio, C_1-C_6alkylsulfinyl, halo-C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, halo-C_1-C_6alkylsulfonyl, C_3-C_6cycloalkyl, C_3-C_6cycloalkyl-C_1-C_6alkyl, C_3-C_6cycloalkoxy, C_3-C_6cycloalkoxy-C_1-C_6alkyl, amino, C_1-C_6alkylamino, di-(C_1-C_6alkyl)amino, C_1-C_6alkoxycarbonylamino, cyano, formyl and C_1-C_6alkylcarbonyl, or is substituted at two adjacent carbon atoms by -O-CH_2-O- or -O-CF_2-O-; and

R13 and R8, taken together, represent, together with the three-membered moiety -N-C-C-, to which they are attached, a five-, six-, seven- or eight-membered, partially or fully unsaturated, optionally substituted, heterocyclic ring, which contains 1 ring nitrogen atom and optionally either 1 further ring nitrogen, oxygen or sulfur atom or 2 further ring nitrogen atoms, in which heterocyclic ring each ring oxygen or sulfur atom is bonded to 2 ring carbon atoms, the optional substituents of the said heterocyclic ring being selected from the group consisting of halogen, C_1-C_6alkyl, halo-C_1-C_6alkyl, hydroxy-C_1-C_6alkyl, C(O)-C_1-C_6alkyl and oxo,

in free form or in salt form.

If at least one asymmetrical carbon atom is present in a compound of the formula I, such a compound may exist in optically active form or in the form of mixtures of optical isomers, e. g. in the form of racemic mixtures. All optical isomers and their mixtures, including the racemic mixtures, are part of the present invention.

Compounds of formula I are useful as vanilloid antagonists, that is, they exhibit human vanilloid antagonist activity, and, more particularly, they demonstrate antagonism at the TRPVI receptor. As such they are indicated in the treatment of diseases and conditions in which vanilloid receptor activity plays a role or is indicated.

In the compounds of formula I, certain substituents may be preferred, independently, collectively, or in any combination or sub-combination.

For example, ---- is preferably a double bond.

In certain embodiments, in the compound of formula I, R_2 may preferably be C_1-C_8alkyl or cycloalkyl, more preferably C_1-C_6 alkyl, for example C_1-C_4 alkyl. One particularly preferred value for R_2 is isopropyl. In other embodiments, R_2 may preferably be NH_2 or C_2-C_6alkenyl, for example C_2-C_4alkenyl, such as isopropenyl. When R_2 is a heterocyclic ring as described above it is preferably 5- or 6- membered with one or two heteroatoms selected from N, O and S; a preferred subsituent for the heterocyclic ring is C_1-C_6alkyl, for example C_1-C_4alkyl such as methyl; where the heterocyclic ring is attached to the quinazolinone ring via C_1-C_6alkyl, C_1-C_4alkyl such as propyl, ethyl, and, most preferably methyl, is preferred. Examples of suitable heterocyclic rings include pyridine, furanyl, isoxazole, pyrrolidone, imidazole, thiophene, morpholine, pyrazine, pyrrole, piperidine and thiazole;

When R_3 is C_1–C_6alkyl, (NC)-C_1–C_6alkyl-, R_9-O-(C_1–C_6alkyl)-, R_9-O-(C_1–C_6alkyl)-O-(C_1–C_6alkyl)-,$R_{10}R_{11}$N-(C_1–C_6alkyl)-, $R_{10}R_{11}$N-(C=O)-(C_1–C_6alkyl)-, or (C_1–C_6alkyl)-SO_2-(C_1–C_6alkyl)-, wherein R_9, R_{10} and R_{11} are each independently H or C_1-C_6 alkyl, it may preferably be one of the following:

C_1–C_6alkyl, for example C_1–C_4alkyl, such as isopropyl, propyl, methylbutyl;
(NC)-C_1–C_6alkyl-, for example (NC)-C_1–C_4alkyl, such as acetonitrile;
R_9-O-(C_1–C_6alkyl), for example R_9-O-(C_1–C_4alkyl), such as hydroxyethyl, methoxyethyl;
$R_{10}R_{11}$N-(C_1–C_6alkyl)-, for example $R_{10}R_{11}$N-(C_1–C_4alkyl)-, such as dimethylaminoethyl, methylaminoethyl;
$R_{10}R_{11}$N-(C=O)-(C_1–C_6alkyl)-, such as $R_{10}R_{11}$N-(C=O)-(C_1–C_4alkyl), such as dimethylacetamide;
R_9-O-(C_1–C_6alkyl)-O-(C_1–C_6alkyl)-, such as R_9-O-(C_1–C_4alkyl)-O-(C_1–C_4alkyl)-, such as hydroxyethoxyethyl;
(C_1–C_6alkyl)-SO_2-(C_1–C_6alkyl)-, such as (C_1–C_4alkyl)-SO_2-(C_1–C_4alkyl)-, such as methylsulfonylethyl;

when R_3 is unsubstituted phenyl or phenyl substituted according to the above, it may preferably be one of the following:
unsubstituted phenyl;
C_1-C_6 alkoxy phenyl, for example C_1-C_4 alkoxy phenyl, such as methoxyphenyl; or
Phenyl substituted by halogen according to the above; such as phenyl substituted with halogen, for example chlorine, and with $R_{10}R_{11}$N-(C_1–C_6alkyl)-, for example $R_{10}R_{11}$N-(C_1–C_4alkyl)-, such as dimethylaminomethyl, or phenyl substituted three or four times wherein the substituents are selected from halo, for example choro and fluoro, hydroxyl, methoxy, trifluoromethyl and methyl;
Phenyl substituted with a 5- or 6-membered saturated or unsaturated heterocyclic ring having one, two or three heteroatoms selected from N, O and S, for example oxazole, or
Phenyl substituted with halo-substituted phenyl, for example fluoro-biphenyl;

when R_3 is cycloalkyl as defined above it may preferably be one of the following:
C_3-C_6 cycloalkyl directly attached to the quinzolinone ring, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;
C_3-C_6 cycloalkyl attached to the quinzolinone ring via C_1–C_6alkyl, for example C_1–C_4alkyl, such as propyl, isopropyl, ethyl or, particularly, methyl;

Substituted C_3-C_6 cycloalkyl having for example a single substitutent selected from –(C=O)OR_9, for example –(C=O)OC_1-C_6alkyl such as –(C=O)OC_1-C_4alkyl, for example –(C=O)OMe or, particularly, –(C=O)OEt;

when R_3 is benzyl, or phenyl(C_1 –C_6alkyl)-, phenoxy-(C_1 –C_6alkyl)- or phenyl(C=O)-(C_1 –C_6alkyl)-, each as defined above, it may preferably be one of the following:
benzyl;
benzyl substituted by one or two substituents selected from C_1-C_6alkyl, for example C_1-C_4 alkyl such as methyl, C_1-C_6alkoxy, for example C_1-C_4 alkoxy such as methoxy,
phenylethyl;
phenylpropyl;
phenyl(C=O)-(C_1 –C_6alkyl)-, for example phenyl(C=O)-(C_1 –C_4alkyl)-, such as –CH_2-(C=O)-Ph;

when R_3 is a 5, 6, or 7- membered, saturated or unsaturated, heterocyclic ring, as defined above, it may preferably be one of the following:
i) a 5-or 6-membered, saturated or unsaturated, heterocyclic ring directly attached to the quinazolinone ring;
ii) a 5-or 6-membered, saturated or unsaturated, heterocyclic ring attached to the quinazolinone ring via a methyl or ethyl linker;
iii) a 5-or 6-membered, saturated or unsaturated, heterocyclic ring directly attached to the quinazolinone ring or attached to the quinazolinone ring via a methyl or ethyl linker, containing one or two heteroatoms selected from N, O and S;
iv) any of i)-iii) above substituted with a substituent selected from cyano, C_1 –C_6alkyl, for example C_1 –C_4alkyl, such as ethyl or, particularly, methyl, halo, for example fluoro or, particularly, chloro, halo phenyl, for example fluoro- or, particularly, chlorophenyl; R_9-O-(C=O)-, for example C(O)OMe or, particularly, C(O)OEt, or =O;
v) any of i)-iv) above wherein the 5-or 6-membered, saturated or unsaturated, heterocyclic ring is selected from pyridine, furanyl, isoxazole, pyrrolidone, imidazole, thiophene, morpholine, pyrazine, pyrrole, piperidine and thiazole;

when R_3 is a 9- or 10- membered aromatic or heterocyclic fused ring as described above, it may preferably be one of the following:

i) a 9- or 10- membered aromatic or heterocyclic fused ring having zero, one or two heteroatons selected from N, O and S;
ii) a 9- or 10- membered aromatic or heterocyclic fused ring according to i) directly attached to the quinazolinone ring;
iii) a 9- or 10- membered aromatic or heterocyclic fused ring according to i) attached to the quinazolinone ring via a methyl or ethyl linker;
iv) a 9- or 10- membered aromatic or heterocyclic fused ring according to ii) or iii) optionally substituted with a substituent selected from halo, for example fluoro or, preferably, chloro, or hydroxyl;
v) a 9- or 10- membered aromatic or heterocyclic fused ring according to ii), iii) or iv), selected from naphthalene, benzothiazole, benzodioxole and quinoline;

and when R_3 is selected from group (a'), it is preferably phenyl substituted by chloro, bromo, C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy or (C_3-C_6cycloalkyl)C_1-C_4alkoxy;

R_5 is most preferably hydrogen or hydroxyl.

R_6 is most preferably hydrogen or hydroxyl;

R12 is preferably hydrogen, formyl, C_1-C_6alkylcarbonyl or benzyl, the phenyl group of which is optionally substituted by 1, 2 or 3 substituents, selected from the group consisting of halogen, C_1-C_6alkyl, halo-C_1-C_6alkyl, hydroxy, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, halo-C_1-C_6alkoxy, C_1-C_6alkylthio, halo-C_1-C_6alkylthio, C_1-C_6alkylsulfinyl, halo-C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, halo-C_1-C_6alkylsulfonyl, C_3-C_6cycloalkyl, C_3-C_6cycloalkyl-C_1-C_6alkyl, C_3-C_6cycloalkoxy, C_3-C_6cycloalkoxy-C_1-C_6alkyl, amino, C_1-C_6alkylamino, di-(C_1-C_6alkyl)amino, C_1-C_6alkoxycarbonylamino, cyano, formyl and C_1-C_6alkylcarbonyl, or is substituted at two adjacent carbon atoms by -O-CH_2-O- or -O-CF_2-O-,
preferably hydrogen, formyl, C_1-C_6alkylcarbonyl or benzyl,
more preferably hydrogen or formyl,
preferably hydrogen;

R13 and R8, taken together, may preferably represent, together with the three-membered moiety -N-C-C-, to which they are attached, a five-, six-, seven- or eight-

membered, partially or fully unsaturated, optionally substituted, heterocyclic ring, which contains 1 ring nitrogen atom and optionally either 1 further ring nitrogen, oxygen or sulfur atom or 2 further ring nitrogen atoms, in which heterocyclic ring each ring oxygen or sulfur atom is bonded to 2 ring carbon atoms, the optional substituents of the said heterocyclic ring being selected from the group consisting of halogen, C_1-C_6alkyl, halo-C_1-C_6alkyl, hydroxy-C_1-C_6alkyl, C(O)-C_1-C_6alkyl and oxo, or

R13 and R8, taken together, represent, together with the three-membered moiety -N-C-C-, to which they are attached, a five-, six- or seven-membered, partially or fully unsaturated, optionally substituted, heterocyclic ring, which contains 1 ring nitrogen atom and optionally either 1 further ring nitrogen, oxygen or sulfur atom or 2 further ring nitrogen atoms, in which heterocyclic ring each ring oxygen or sulfur atom is bonded to 2 ring carbon atoms, the optional substituents of the said heterocyclic ring being selected from the group consisting of halogen, C_1-C_6alkyl, C(O)-C_1-C_6alkyl, halo-C_1-C_6alkyl, hydroxy-C_1-C_6alkyl and oxo, or

N-R13 and R8-, taken together, represent a moiety N-X-O- (Ibb), in which -X- is -C(=O)- or -$(CH_2)_a$-, in which a is 2 or 3 and in which any methylene group, independently from any other methylene group in the moiety Ibb, is, optionally, mono-substituted by oxo or substituted by 1 or 2 substituents, selected from the group consisting of halogen, C_1-C_6alkyl, C(O)-C_1-C_6alkyl, halo-C_1-C_6alkyl and hydroxy-C_1-C_6alkyl, or N-R13 and R8-, taken together, represent a moiety N-C(R_a)=C(R_b)- (Idd), in which R_a is hydrogen, C_1-C_6alkyl, halo-C_1-C_6alkyl or hydroxy-C_1-C_6alkyl and R_b is hydrogen, C_1-C_6alkyl, halo-C_1-C_6alkyl or hydroxy-C_1-C_6alkyl, or N-R13 and R8-, taken together, represent a moiety N-C(R_c)=N- (Iee), in which R_c is hydrogen, C_1-C_6alkyl or halo-C_1-C_6alkyl, or N-R13 and R8-, taken together, represent a moiety N-N=C(R_d)- (Iff), in which R_d is hydrogen, C_1-C_6alkyl or halo-C_1-C_6alkyl, or N-R13 and R8-, taken together, represent a moiety N-N=C(R_f)- (Ig), in which R_f is halogen, or N-R13 and R8-, taken together, represent a moiety N-N=N- (Ih) or N-R13 and R8-, taken together, represent a moiety N-$(CH_2)_2$-N(H)-C(R_g)H- (Iii), in which R_g is hydrogen, C_1-C_6alkyl or halo-C_1-C_6alkyl,

preferably N-R13 and R8-, taken together, represent a moiety N-X-O- (Ibb), in which -X- is -C(=O)- or -$(CH_2)_a$-, in which a is 2 or 3 and in which any methylene group, independently from any other methylene group in the moiety Ibb, is optionally substituted by 1 or 2 substituents, selected from the group consisting of C_1-C_6alkyl and hydroxy-C_1-C_6alkyl, or N-R13 and R8-, taken together, represent a moiety N-

$C(R_a)=C(R_b)$- (Idd), in which R_a is hydrogen and R_b is C_1-C_6alkyl, or N-R13 and R8-, taken together, represent a moiety N-$C(R_c)$=N- (Iee), in which R_c is hydrogen, C_1-C_6alkyl or halo-C_1-C_6alkyl, or N-R13 and R8-, taken together, represent a moiety N-N=$C(R_d)$- (Iff), in which R_d is hydrogen or C_1-C_6alkyl, or N-R13 and R8-, taken together, represent a moiety N-N=$C(R_f)$- (Ig), in which R_f is halogen, or N-R13 and R8-, taken together, represent a moiety N-N=N- (Ih) or N-R13 and R8-, taken together, represent a moiety N-$(CH_2)_2$-N(H)-$C(R_g)$H- (Iii), in which R_g is hydrogen.

"C_1-C_8alkyl" denotes straight-chain or branched C_1 to C_6-alkyl; "C_1-C_6alkyl" denotes straight-chain or branched C_1 to C_6-alkyl; and "C_1-C_4alkyl" denotes straight-chain or branched C_1 to C_6-alkyl;e.g., methyl ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl or *tert*-butyl.

"C_2-C_6alkenyl" denotes straight-chain or branched C_2 to C_6-alkenyl, e.g., ethenyl, *n*-propenyl or isopropenyl.

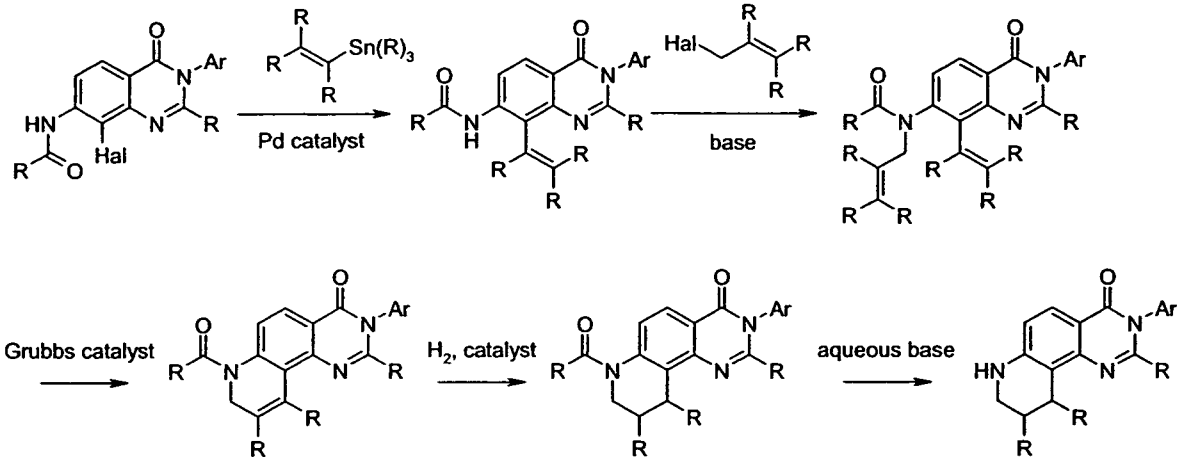
"C_1-C_6alkoxy" denotes straight-chain or branched C_1 to C_6-alkyl-oxy, e.g., methoxy, ethoxy, *n*-propoxy or isopropoxy.

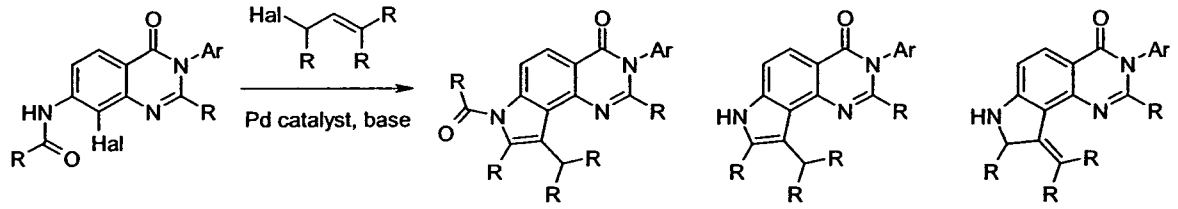
"Halo" denotes halogen which may be I, Br, Cl or F.

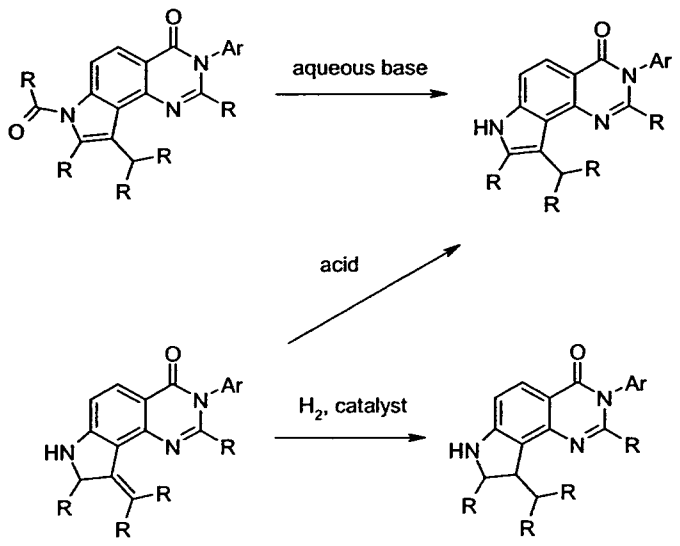
"Esterified hydroxy" denotes acyloxy, preferably C_1-C_6alkanoyloxy, more preferably C_1-C_4alkanoyloxy.

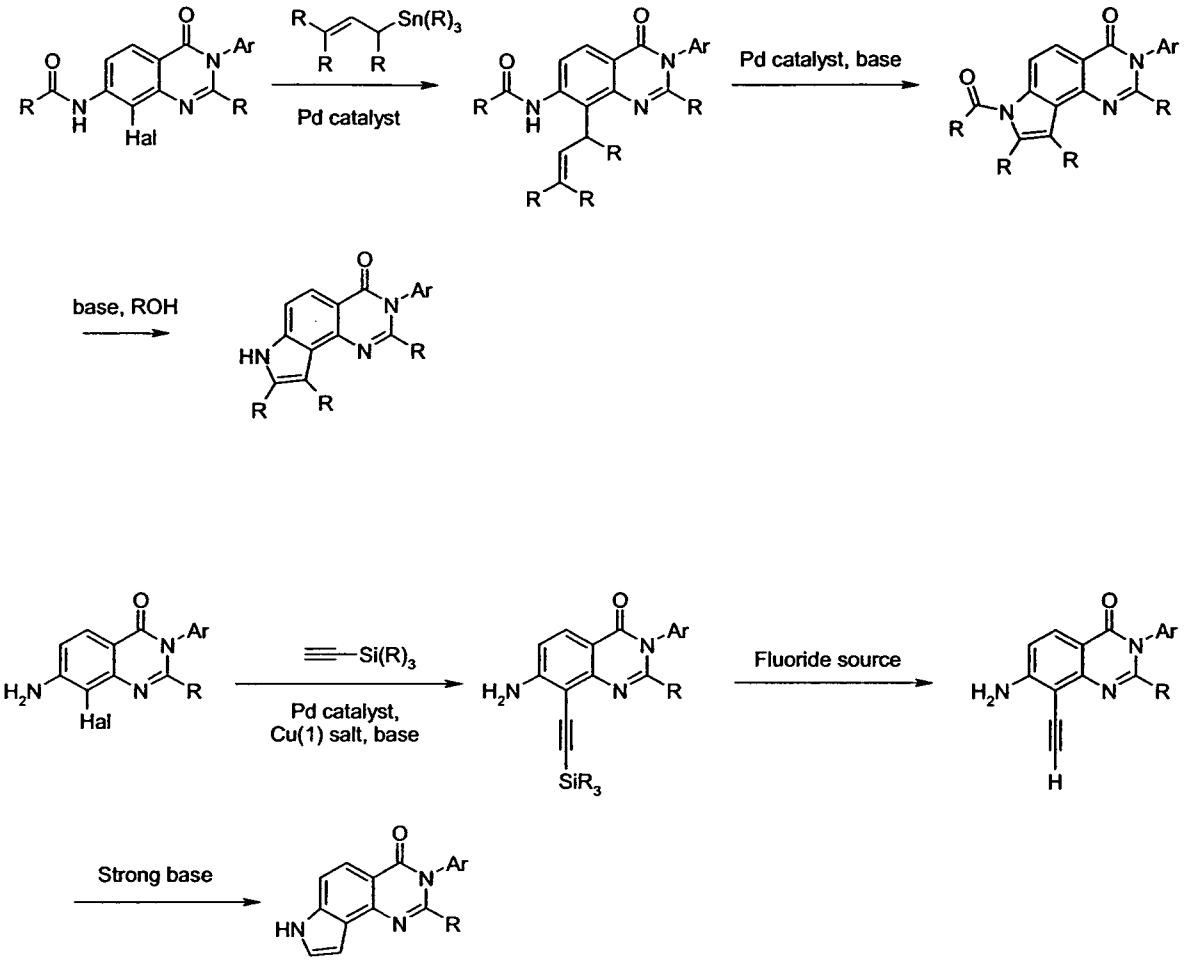
"Etherified hydroxy" denotes C_1-C_6alkoxy, preferably C_1-C_4alkoxy.

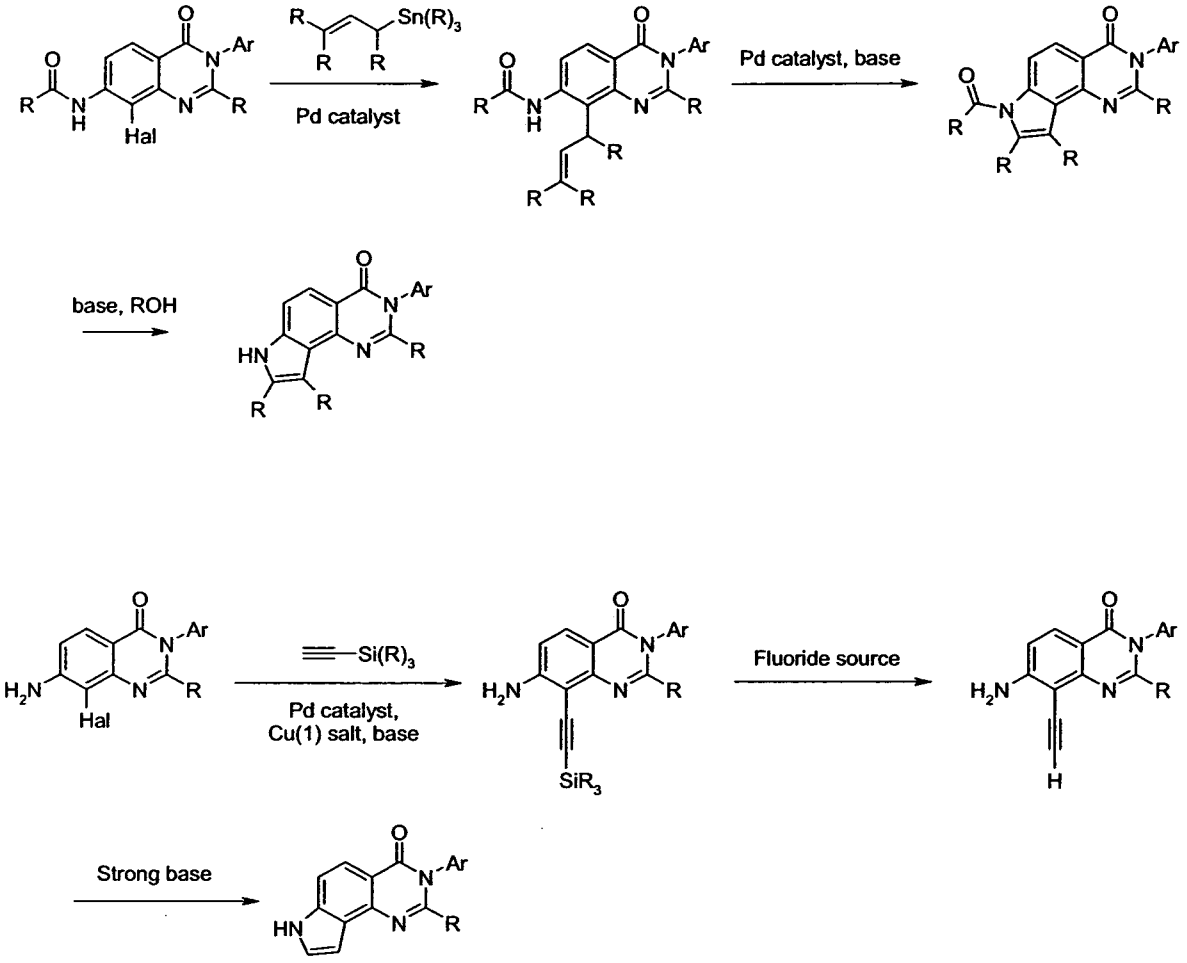
The quinazolinone compounds of the invention exist in free or salt form. The invention is to be understood as including the compounds of formula (I) in free or salt form. The present invention also relates to a process for the preparation of a compound of formula I, in free form or in salt form, according to the following representative reaction schemes, in which "Ar" denotes R_3 as defined above.

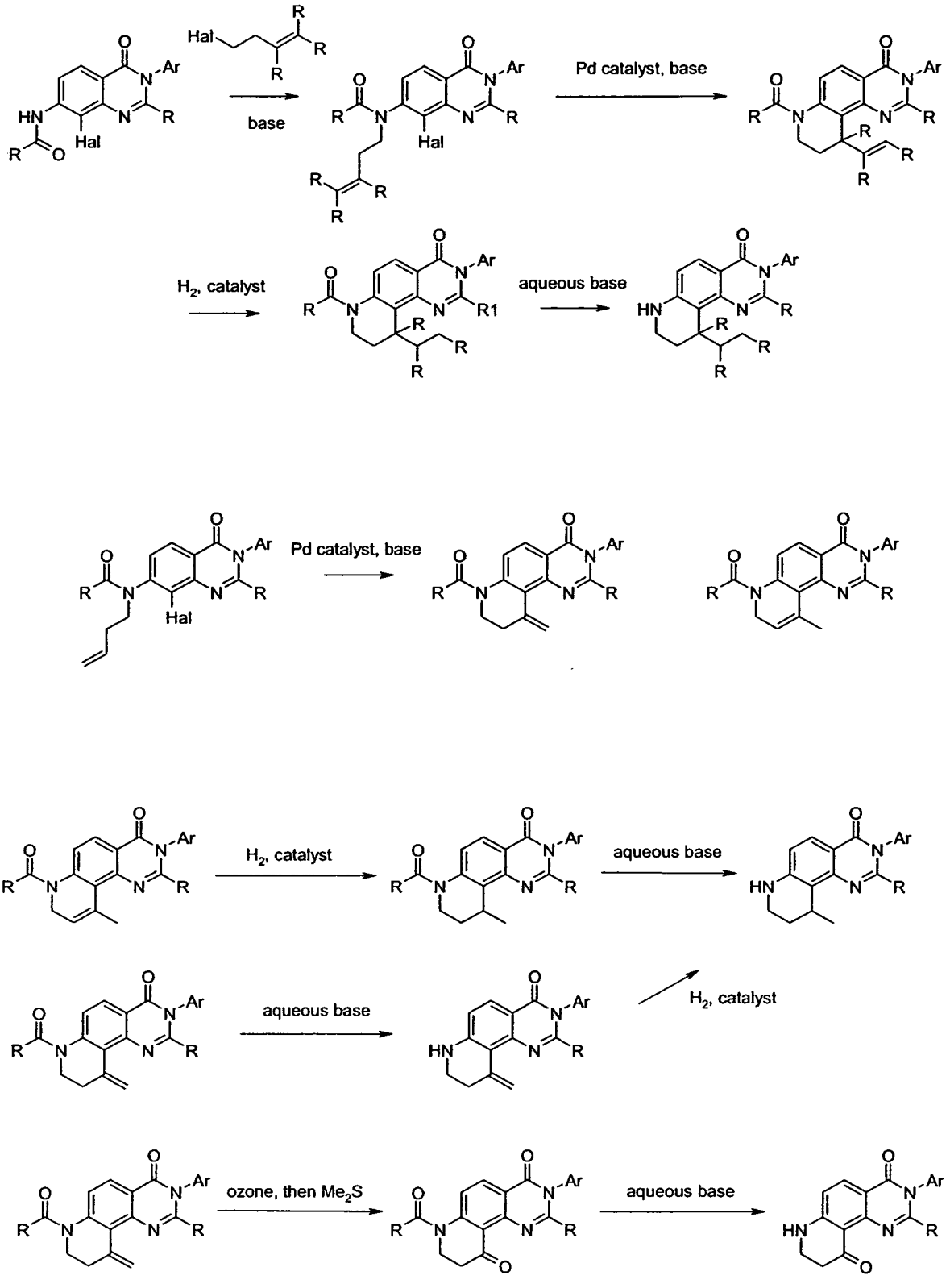

Pd catalyst
base
Grubbs catalyst
H_2, catalyst
aqueous base

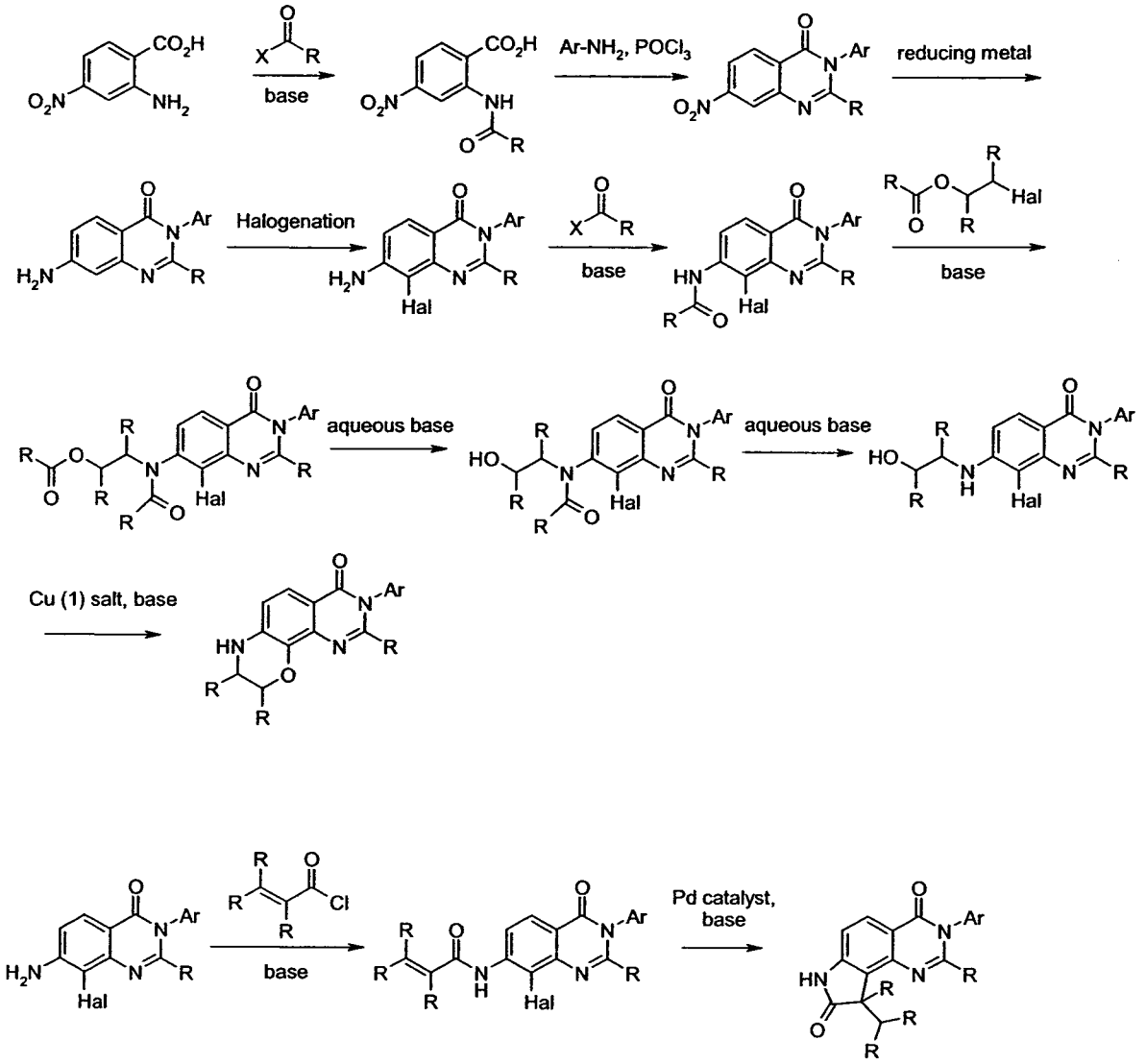

Pd catalyst, base


aqueous base
acid
H_2, catalyst


Sn(R)3
Pd catalyst
Pd catalyst, base
base, ROH
Hal
Si(R)3
Pd catalyst,
Cu(1) salt, base
Fluoride source
Strong base


Sn(R)3
Pd catalyst
Pd catalyst, base
base, ROH
Hal
Si(R)3
Pd catalyst,
Cu(1) salt, base
Fluoride source
Strong base


Hal
R
base
Pd catalyst, base
H2, catalyst
aqueous base
R1
Ar
HN
O
N



In the above schemes, R can be alkyl or another suitable group.

Detailed reaction conditions are described in the Examples.

The working-up of the reaction mixtures and the purification of the compounds thus obtainable may be carried out in accordance with known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice-versa.

Compounds of formula (I) in optically pure form can be obtained from the corresponding racemates according to well-known procedures, e.g., HPLC with chiral matrix. Alternatively, optically pure starting materials can be used.

Stereoisomeric mixtures, e.g., mixtures of diastereomers, can be separated into their corresponding isomers in a manner known per se by means of suitable separation methods. Diastereomeric mixtures, e.g., may be separated into their individual diastereomers by means of fractionated crystallisation, chromatography, solvent distribution and similar procedures. This separation may take place either at the level of a starting compound or in a compound of formula (I) itself. Enantiomers may be separated through the formation of diastereomeric salts, e.g., by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, e.g., by HPLC, using chromatographic substrates with chiral ligands.

In any additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected, e.g., by one or more of the protecting groups mentioned below. The protecting groups are then wholly- or partly-removed according to one of the methods described there.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e., without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, e.g., under conditions analogous to physiological conditions, and that they are not present in the end-products. The skilled artisan knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove and hereinafter.

The protection of such functional groups by protecting groups, the protecting groups themselves, and their removal reactions are described, e.g., in standard reference works, such as J.F.W. McOmie, *Protective Groups in Organic Chemistry*, Plenum Press, London and NY (1973); T.W. Greene, *Protective Groups in Organic Synthesis*, Wiley, NY (1981); *The Peptides*; Volume 3, E. Gross and J. Meienhofer, Eds., Academic Press, London and NY (1981); *Methoden der organischen Chemie* (*Methods of organic chemistry*), Houben Weyl, 4th Edition, Volume 15/1, Georg

Thieme Verlag, Stuttgart (1974); H.D. Jakubke and H. Jescheit, *Aminosauren, Peptide, Proteine* (*Amino acids, peptides, proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel (1982); and Jochen Lehmann, *Chemie der Kohlenhydrate: Monosaccharide und Derivate* (*Chemistry of carbohydrates: monosaccharides and derivatives*), Georg Thieme Verlag., Stuttgart (1974).

All process steps described herein can be carried out under known reaction conditions, preferably under those specifically mentioned, in the absence of or usually in the presence of solvents or diluents, preferably such as are inert to the reagents used and able to dissolve these, in the absence or presence of catalysts, condensing agents or neutralizing agents, e.g., ion exchangers, typically cation exchangers, e.g., in the H^+ form, depending on the type of reaction and/or reactants at reduced, normal or elevated temperature, e.g., in the range from -100°C to about 190°C, preferably from about -80°C to about 150°C, e.g., at -80°C to 60°C, at room temperature, at -20°C to 40°C or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, e.g., under argon or nitrogen.

Another aspect of this invention relates to the fact that the compounds of formulae (I) and and their pharmaceutically acceptable salts, have beneficial pharmacological activity and, therefore, are useful as pharmaceuticals. In particular, the compounds of formula (I)exhibit human vanilloid antagonistic activity. More particularly, the compounds of formula (I)are active at the TRPVI receptor as demonstrated by their ability to inhibit capsaicin and/or low pH activation of the TRPVI ion channel as follows:

Chinese Hamster Ovary-K1 (CHO-K1) cells, transfected to express either the human, rat or guinea pig TRPV1 receptor, are grown in Minimal Essential Media (MEM) alpha medium without nucleosides supplemented with fetal calf serum (10%), 2 mM L-glutamine, 100 IU/mL penicillin, 100 µg/mL streptomycin and 350-700 µg/mL geneticin. All reagents are supplied by Invitrogen. Cells are grown in T-175 flasks or clear bottom 96- or 384-well plates and maintained at 37°C in a 90% humidified incubator with an atmosphere of 5% CO_2 and 95% air. The cells are passaged twice a week and for experimentation, cells are harvested at approximately 80%

confluency and plated onto view plates at 35,000-40,000 cells per well in 100 µL media and grown overnight.

Calcium mobilisation assay

On the day of the assay, media is aspirated and cells are washed with 10 mM *N*-2-(hydroxyethylpiperazine-*N*'-[2-ethane-sulfonic acid] (HEPES) buffered Hank's Balanced Salt Solution (HBSS), pH 7.4. Cells are then incubated with a fluorescent sensitive-calcium binding dye, typically fluo-4/AM (from Molecular Probes), made up in HEPES buffered HBSS, containing pluronic F-127 with or without probenicid. For the pH assay, HEPES is omitted and the pH of HBSS adjusted to 7.4. After washing, cells are incubated with test compounds (made up in HBSS, pH 7.4), in duplicate. The TRPV1 receptor is stimulated by addition of either capsaicin at an approximate EC_{80} concentration or a low pH buffered solution [60 mM 2-[*N*-morpholino] ethane sulfonic acid (MES) in HBSS] to give a final pH of 5.5. The cellular responses are followed in fluorescent plate reader, typically a Molecular Devices Flexstation. The response in the presence of the antagonist is calculated as a percentage of the control response to capsaicin or low pH and is plotted against the concentration of antagonist. The IC_{50} values (concentrations of antagonist that inhibit responses to either pH 5.5 or capsaicin by 50%) is estimated by non-linear regression analysis to sigmoidal-logistic curves. These values are averaged (means and standard error of the mean) for at least three independent experiments.

A specific example of a calcium mobilization assay is as follows:

On the day of the capsaicin assay, media is aspirated and cells are washed with 100 µL 10 mM *N*-2-(hydroxyethylpiperazine-*N*'-[2-ethane-sulfonic acid] (HEPES) buffered Hank's Balanced Salt Solution (HBSS), pH 7.4. Cells are then incubated for 40-60 minutes with 2.3 µM of the calcium binding dye fluo-4/AM (from Molecular Probes), made up in HEPES buffered HBSS, containing 0.01% pluronic F-127 and 2mM probenicid. For the pH assay, HEPES is omitted and the pH of HBSS adjusted to 7.4. After washing twice with 100 µL assay buffer, cells are incubated for 10 minutes with 100 µL of test compounds (made up in HBSS, pH 7.4), in duplicate. The plate is then placed in a Molecular Devices Flexstation. The TRPV1 receptor is stimulated by application of either capsaicin or low pH. For testing the effect of compounds for possible antagonism, capsaicin is used at an approximate EC_{80}

concentration of 0.05 μM. For pH experiments, a low pH buffered solution [60 mM 2-[*N*-morpholino] ethane sulfonic acid (MES) in HBSS] is added to the assay wells to give a final pH of 5.5.

For determinations of antagonist IC_{50} values (concentrations of antagonist that inhibit responses to either pH 5.5 or capsacin by 50%), at least 10 antagonist concentrations are measured in duplicate. The response in the presence of the antagonist is calculated as a percentage of the control response to capsaicin or low pH and is plotted against the concentration of antagonist. The IC_{50} is estimated by non-linear regression analysis to sigmoidal-logistic curves by Activity-Base software (v5.0.10) or Microcal Origin (v7.03). These values are averaged (means and standard error of the mean) for at least three independent experiments.
The agents of the invention are useful in the prevention and treatment of diseases and conditions in which human VR1 activation plays a role or is implicated, and therefore susceptible to treatment by the modulation (preferably antagonism) of VR1 receptors. Such conditions include, in particular, acute or chronic pain of somatic or visceral origin, inflammatory or obstructive airways disease, urinary incontinence or over-active bladder, inflammatory skin diseases, inflammatory disorders of the gastrointestinal tract, diabetes, obesity and obesity-related diseases, psychiatric disorders, and treatment of the consequences exposure to VR1 agonists.

The agents of the invention are particularly useful in the treatment or prevention of chronic pain with an inflammatory component such as rheumatoid arthritis; bone and joint pain (osteoarthritis); post-surgical or trauma pain including dental pain e.g. following third molar extraction, post mastectomy pain and pain associated with sprains or fractures; musculo-skeletal pain such as fibromyalgia; myofascial pain syndromes; headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain; ear pain; episiotomy pain; burns, and especially primary hyperalgesia associated therewith; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, abdominal pain, gynaecological pain, such as dysmenorrhoea, and labour pain; hemorrhoids; pain associated with the urogenital tract such as cystitis and vulvadynia; chronic pain associated with nerve injury and/or diseases affecting the nervous system, such as neuropathic pain associated with post-herpetic neuralgia, diabetic neuropathy,

chemotherapy-induced neuropathy, amputations ("phantom limb pain"), nerve entrapment and brachial plexus avulsions, low back pain, sciatica and ankylosing spondylitis, reflex sympathetic dystrophy and other chronic nerve injuries; complex regional pain syndromes; Glossodynia or burning mouth syndrome; central nervous system pain, such as pain due to spinal cord or brain stem damage, multiple sclerosis or stroke; gout; scar pain; pain associated with carcinoma, often referred to as cancer pain; pain associated with viral (e.g. HIV)-induced neuropathy, alcohol and narcotic abuse; pain and other symptoms associated with sun or UV burn, exposure to VR1 agonist (e.g. capsaicin, acid, tear gas, noxious heat or pepper spray), snake, spider or insect bite and jellyfish sting.

Gastrointestinal disorders to be treated in accordance with the invention include those associated with gastrointestinal hypersensitivity, visceral pain and/ or altered motor responses (including electrolyte/water secretion) such as functional bowel disorders and functional gastrointestinal disorders, including irritable bowel syndrome (IBS), functional dyspepsia, heartburn, non-erosive reflux disease, intestinal pseudoobstruction, functional abdominal bloating, and functional abdominal pain; other conditions associated with visceral hypersensitivity including gastro-oesophageal reflux disease and emesis, oesophagitis, post-operative visceral pain, post-operative ileus, visceral smooth muscle spasms, ulcerative colitis, Crohn's disease, ulcers, chronic constipation, diarrhea, early satiety, epigastric pain, nausea, vomiting, burbulence, anal incontinence, faecal urgency and rectal hypersensitivity, gastroparesis, e. g. diabetic gastroparesis, pancreatitis and Hirschsprung's disease.

Urinary incontinence ("UI") or overactive bladder to be treated in accordance with the invention is a broad term that covers a range of disorders and symptoms including urge UI, stress UI, mixed urge/stress UI, neurogenic UI, bladder detrusor hyperreflexia (neurogenic detrusor overactivity), detrusor instability (idiopathic detrusor overactivity), decreased bladder compliance, weakness of urethal sphincter, urinary outlet obstruction, interstitial cystitis, nephritis, uveitis, sensory urgency, motor urgency, nocturia, and bladder-related visceral pain.

The agents of the invention are also useful as agents for the therapy of hyperreactive, inflammatory or obstructive airways diseases including asthma,

inflammatory airways disease, e.g. chronic obstructive pulmonary or airways disease (COPD or COAD), adult respiratory distress syndrome (ARDS), chronic bronchitis, pneumoconiosis, e.g. aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis; rhinitis including allergic rhinitis such as seasonal and perennial rhinitis, and non-allergic rhinitis; cough, either idiopathic or associated with respiratory diseases such as COPD, asthma, cystic fibrosis, cancer, or gastrointestinal disturbances such as gastro-oesophageal reflux.

The agents of the invention may also have therapeutic benefit in inflammatory skin disorders, for example psoriasis and eczema, or itch of non-specific origin; contact dermatitis and hypersensitivity; autoimmune or inflammatory diseases, including Crohn's disease, ulcerative colitis and Gullian Barre Syndrome; multiple chemical sensitivity, neurological diseases like anxiety, panic disorders, depression, schizophrenia, cognition, Parkinson's Disease and Alzheimer's Disease; hair loss; diabetes; obesity and obesity-related diseases; as anti-spasmodics, e.g. for the treatment of spasm of the gastrointestinal tract or uterus; for the therapy of septic shock, e.g. as anti-hypovolaemic and / or anti hypotensive agents; cerebral oedema.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, e.g., the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.05 to about 150, preferably from about 0.1 mg/kg to about 100 mg/kg animal body weight. In larger mammals, e.g., humans, an indicated daily dosage is in the range from about 0.5 to about 5,000, preferably from about 1 mg to about 500 mg of a compound of formula (I), conveniently administered, e.g., in divided doses up to four times a day or in sustained-release form.

The agents of the invention can be administered in vivo either alone or in combination with other pharmaceutical agents, e.g. agents effective in the treatment of diseases and conditions in which the human VR1 activation plays a role or is implicated. A suitable combination consists of a compound of the present invention with a compound selected from the class or individuals from the following list: Dopamine D_2 antagonists, eg domperidone, metoclopramide and itopride; $5HT_4$ receptor agonists, eg cisapride, cinitapride, mosapride, renzapride, prucalopride, tegaserod, and compounds described in WO 2005068461 (Aryx), e.g.

AT-7505, US 2005228014 and WO 2005080389 (Theravance), e.g. TDI-2749, US 2006100426, US 2006100236, US 2006135764, US 20060183901, WO 200610827, WO 2006094063, WO 2006090224, WO2006090279, US 2005277671, WO 2005092882, WO 2005073222, JP 2005104896, JP 2005082508, WO 2005021539, JP 2004277319, JP 2004277318, WO 2004026869 and EP 1362857;

$5HT_3$ agonists, eg pumosetrag;

CCK_A receptor antagonists, eg loxiglumide and dexloxiglumide;

Motilin receptor agonists, eg motilin, atilmotilin, erythromycin, alemcinal, mitemcinal, KOS-2187 and compounds described in WO 2005060693;

μ-opioid antagonists, eg alvimopan and methylnaltrexone;

Opioid agonists, eg asimadoline, loperamide and codeine;

CRF-1 receptor antagonists, eg GSK876008 and compounds described in WO 2004069257, WO 9940089, US 6844351, WO 2005013997, WO 2005014557, WO 2005023806, WO 2005026126, WO 2005028480, WO 2005044793, WO 2005051954, WO 2005051954, WO 2005115399, WO 2005028480, WO 2005023806, WO 2006044958, US 20060211710 and WO 2006108698;

Glutamate receptor antagonists, eg AZD9272 and compounds described in WO 9902497, WO 2000020001, WO 200304758 and WO 2005030723;

Neurokinin receptor antagonists, eg casopitant, nepadutrent saredutant, DNK-333, SLV-317, SLV321, SLV317 and compounds described in EP 96-810237;

$5HT_3$ receptor antagonists, eg alosetron, cilansetron, ramosetron, azasetron, ondansetron, granisetron tropisetron and DDP225;

Histamine H_2 antagonists, eg famotidine, cimetidine, rantidine and nizatidine;

Histamine H_4 antagonists, eg JNJ7777120, JNJ10191584 and compounds described in US 2006111416, WO 2006050965, WO 2005092066, WO 2005054239 US 2005070550, US 2005070527 and EP 1505064;

Proton pump inhibitors, eg omeprazole, lansoprazole, rabeprazole, tentoprazole, pantoprazole, esomeprazole, revaprazan soraprazan and AGN201904;

Chloride channel activators, eg lubiprostone;

Guanylate cyclase activators, eg linaclotide;

Muscarinic antagonists, eg darifenacin, solifenacin, atropine, dicycloverine, hycosine butyl bromide, propantheline, oxybutinin, cimetropium bromide, pinaverium bromide and otilonium bromide;

Antispasmodics, eg mebeverine, tiropramide, alverine and peppermint oil;

Stimulant laxatives, eg bisacodyl;
Osmotic laxatives, eg activated charcoal with sorbitol, lactulose, magnesium hydroxide and phosphate buffered saline;
Faecal softeners, eg senna concentrate, liquid paraffin and arachis oil;
Absorbents and fibre supplements, eg bulk fibre laxatives such as bran, methycellulose, ispaghula husk and sterculia;
Antacids, eg aluminium, magnesium and calcium antacids, simeticone and alginate containing preparations;
GI relaxants, eg cholestyramine resin;
Bismuth compounds, eg bismuth subsalicylate;
Vanilloid receptor antagonists, eg compounds described in WO 2002076946, WO 2004033435, WO 2005121116 and WO 2005120510;
Anticonvulsants, eg carbamazepine, oxcarbemazepine, lamotrigine, gabapentin, and pregabalin;
NSAIDS, eg aspirin, acetometaphen, ibuprofen, diclofenac, naproxen, flurbiprofen, indomethacin, piricoxam, ketoprofen, sulindac and diflunisal;
COX-2 inhibitors eg celecoxib, rofecoxib, lumiracoxib, valdecoxib, etoricoxib and compounds described in WO 2004048314;
Opiates, eg morphine, buprenorphine, diamorphine, dihydrocodeine, fentanyl and pethidine;
$GABA_b$ modulators, eg racemic and (R)-baclofen, AZD3355, XP19986 and compounds described in WO 2006001750 and WO 2004000856;
CB receptor ligands, eg compounds described in WO 2002042248 and WO 2003066603;
Calcium channel blockers, eg ziconotide, AGI0-003, PD-217014 and compounds described in WO 2006038594, WO 2006030211 and WO 2005068448;
Sodium channel blockers, eg lamotrigine and compounds described in WO 2006023757, WO 2005097136, JP 2005206590 and WO 2005047270;
Tricyclic antidepressants, e.g. clomipramine, amoxapine, nortripyline, amitriptyline, imipramine, desipramine, doxepin, trimipramine and protripyline;
Selective serotonin reuptake inhibitors, eg fluoxetine, paroxetine, citaprolam, sertaline, fluvoxamine, duloxetine;
Anxiolytic agents, eg milnacipran, tianeptine, MCI-225 and dextofisopam;
CGRP antagonists, eg olcegepant and cizolirtine;

$5HT_{1d}$ antagonists, eg almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmatriptan; and
Bradykinin receptor antagonists, eg compounds described in WO 2000075107, WO 2002092556 and WO 20050851298.

The pharmaceutical compositions for separate administration of the combination partners and for the administration in a fixed combination, i.e., a single galenical composition comprising at least two combination partners, according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application.

Pharmaceutical compositions contain, e.g., from about 0.1% to about 99.9%, preferably from about 20% to about 60%, of the active ingredients. Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, e.g., those in unit dosage forms, such as tablets including sugar-coated tablets, capsules, suppositories and ampoules. These are prepared in a manner known, per se, e.g., by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of a combination partner contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units.

A further aspect of the instant invention involves the novel compositions comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of a compound of formula (I), in free or salt form.

In accordance with the foregoing, the present invention also provides:

(1) A compound of formula (I) in free or salt form for use as a vanilloid receptor blocker, e.g., for use in any of the particular indications set forth hereinabove;

(2) A compound of formula (I) in free or salt form for the treatment of a disease or condition in which vanilloid receptor plays a role or is implicated;

(3) A method for the treatment of any of the particular indications set forth hereinabove in a subject in need thereof which comprises administering a therapeutically effective amount of a compound of formula (I) in free or salt form;

(4) A method for treating or preventing a disease or condition in which vanilloid receptor plays a role or is implicated comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I) in free or salt form;

(5) Use of a compound of formula (I) in free or salt form for the manufacture of a medicament for the treatment or prevention of a disease or condition in which activity of vanilloid receptor plays a role or is implicated;

(6) A method as set forth hereinabove comprising co-administration, e.g., concomitantly or in sequence, of a therapeutically effective amount of a vanilloid receptor antagonist, e.g., a compound of formula (I) in free or salt form and a second drug substance, said second drug substance being, e.g., for use in any of the particular indications set forth hereinabove; and

(7) A combination comprising a therapeutically effective amount of a compound of formula (I) in free or salt form and a second drug substance, said second drug substance being, e.g., for use in any of the particular indications set forth hereinabove.

Examples

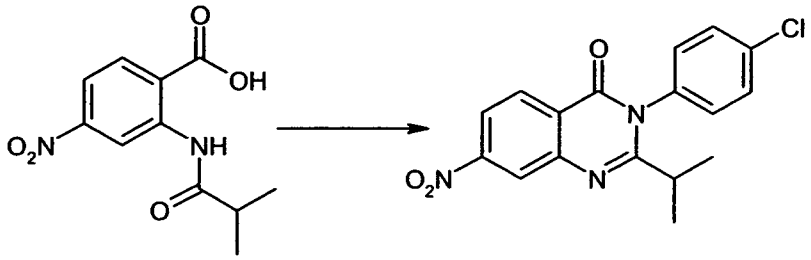
In the Examples which follow, which are not intended to limit, in any way, the scope of the present invention, the following abbreviations are used:

eq.	equivalent(s)
h	hour(s)
min	minute(s)

The HPLC retention time (RT) data correspond to the following conditions: Phenomenex Luna reversed phase C18 3 micron (30 x 4.6 mm) column; column temperature 25°C; gradient elution 10 % MeCN in water (+ 0.08 % formic acid) to 100 % MeCN over 10 minutes (rate = 3.0 ml/minute). The purity values are quoted at 254 nm.

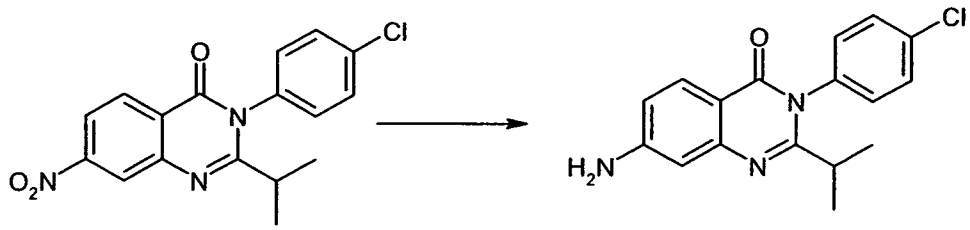
Preparative Examples

3-(4-chlorophenyl)-2-isopropyl-7-nitro-3H-quinazolin-4-one



A suspension of 4-nitroanthranilic acid isobutyramide (4 g, 15.8 mmol), 4-chloroaniline (2.2 g, 17.2 mmol) and phosphorus trichloride (5.6 mL) in toluene (150 mL) was heated to reflux (bath temperature 150 °C) for 2 h. The reaction mixture was allowed to cool to room temperature and then evaporated to dryness. The residue was partitioned between water and EtOAc and the aqueous phase was extracted (x2) with EtOAc. The combined organic phases were washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. Trituration with isopropyl ether provided the title compound as a brown solid (4.2 g, 77%).

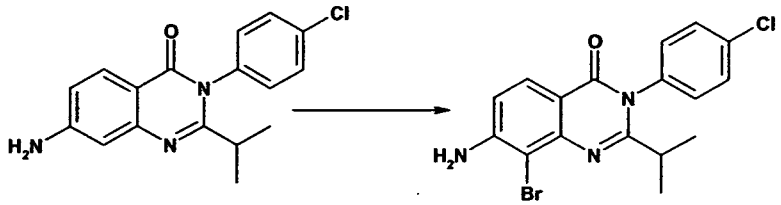
7-Amino-3-(4-chlorophenyl)-2-isopropyl-3H-quinazolin-4-one



A mixture of 3-(4-chlorophenyl)-2-isopropyl-7-nitro-3H-quinazolin-4-one (2.4 g, 6.98 mmol), iron powder (1.16 g, 20.8 mmol) and glacial acetic acid (70 mL) was stirred at 50 °C for 2.5 h. The reaction mixture was allowed to cool to room tremperature and

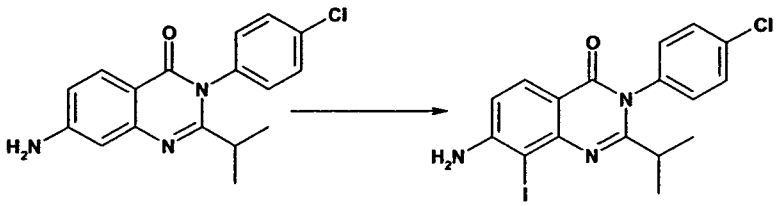
then evaporated *in vacuo* to dryness. The residue was partitioned between water and EtOAc and the aqueous phase was extracted (x2) with EtOAc. The combined organic phases were washed with water, dried (Na_2SO_4) and evaporated *in vacuo* to give a brown solid. Purification by automated flash chromatography (gradient elution: EtOAc/DCM 0 to 50%) provided the title compound as a pale yellow solid (1.74 g, 79%).

7-Amino-8-bromo-3-(4-chloro-phenyl)-2-isopropyl-3H-quinazolin-4-one



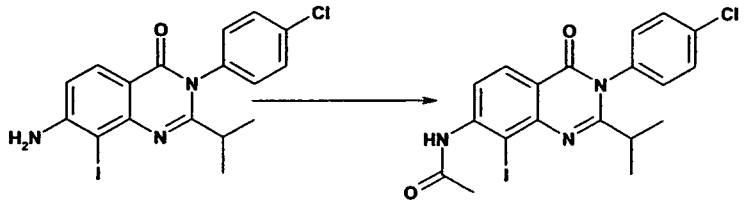
To a solution of 7-Amino-3-(4-chloro-phenyl)-2-isopropyl-3H-quinazolin-4-one (1.0 g, 3.2 mmol) in chloroform (20 ml) was added N-bromosuccinimide. After stirring for 5 minutes at ambient temperature TLC indicated complete conversion. The reaction mixture was diluted with water and dichloromethane, and the aqueous layer was extracted with dichloromethane. The combined aqueous extracts were dried over anhydrous sodium sulfate and evaporated to give a dark brown solid. The crude product was triturated with diethyl ether to provide the title compound as a grey solid, which was recovered by filtration and dried (1.02 g, 2.6 mmol, 81%).

7-Amino-8-iodo-3-(4-chloro-phenyl)-2-isopropyl-3H-quinazolin-4-one



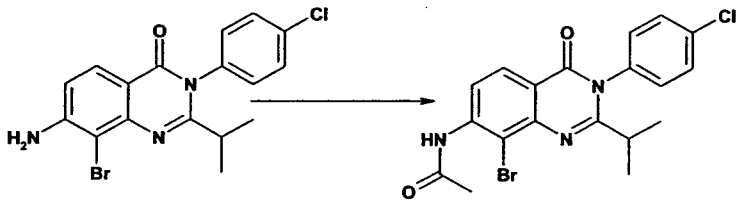
The title compound was prepared in an analogous manner to **7-Amino-8-bromo-3-(4-chloro-phenyl)-2-isopropyl-3H-quinazolin-4-one**, using N-iodosuccinimide instead of N-bromosuccinimide and extending the reaction time to 1.5 h. Purification by automated gradient elution flash chromatography (eluent hexane to hexane/ethyl acetate 7/3) provided the title compound as a pale brown solid, 94%.

N-[3-(4-Chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acetamide



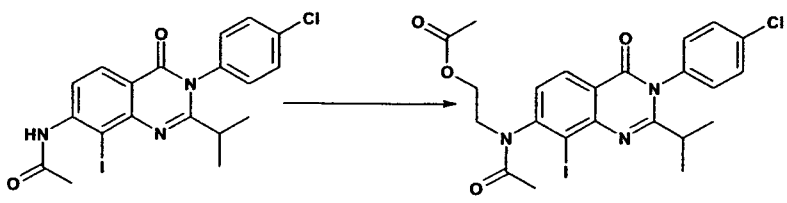
To a solution of 7-Amino-8-iodo-3-(4-chloro-phenyl)-2-isopropyl-3H-quinazolin-4-one (300 mg, 0.682 mmol) in THF/acetic anhydride 20/1 (21 ml) was added concentrated hydrochloric acid (3 drops). The reaction mixture was stirred at room temperature overnight and TLC/LCMS analysis indicated complete conversion. The reaction mixture was diluted with water and extracted with ethyl acetate (x 2). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated to provide the title compound as an off-white solid (320 mg, 0.664 mmol, 97%), which was used without further purification.

N-[8-Bromo-3-(4-chlorophenyl)-2-isopropyl-4-oxo-3,4-dihydroquinazolin-7-yl]-acetamide



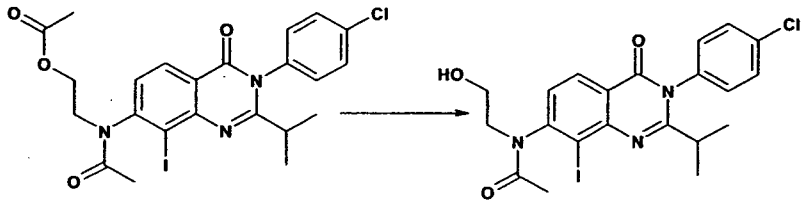
The title compound was prepared in an analogous manner to **N-[3-(4-Chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acetamide.** Yield: 97%

Acetic acid 2-{acetyl-[3-(4-chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-amino}-ethyl ester



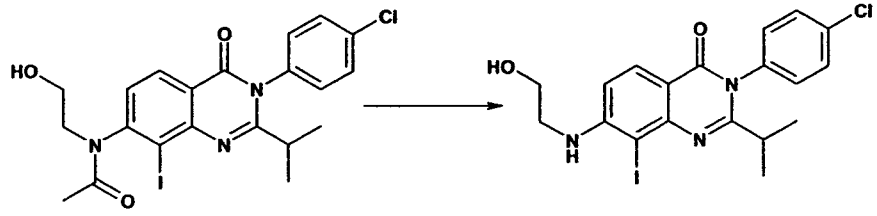
To a solution of N-[3-(4-Chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acetamide (300 mg, 0.622 mmol) in DMF was added sodium hydride (37 mg, 60% dispersion in mineral oil, 0.933 mmol) and the mixture was stirred at ambient temperature for 20 min. 2-Bromoethyl acetate (0.066 ml, 0.933 mmol) was added and stirring was continued overnight. TLC and LCMS analysis indicated incomplete conversion. Cesium carbonate (202 mg, 0.622 mmol), additional 2-bromoethyl acetate (0.044 ml, 0.622 mmol) and potassium iodide (catalytic) were added and stirring was continued for 4 h. TLC and LCMS analysis indicated a trace of starting material remained. The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated. Purification by automated gradient elution flash chromatography (eluent hexane to ethyl acetate) provided the title compound 326 mg, 0.574 mmol, 92%.

N-[3-(4-Chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-N-(2-hydroxyethyl)acetamide



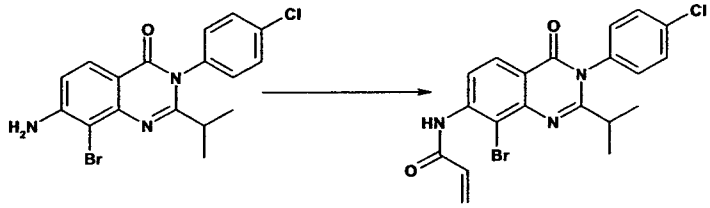
To a solution of acetic acid 2-{acetyl-[3-(4-chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-amino}-ethyl ester (300 mg, 0528 mmol) in methanol/water 2/1 (6 ml) was added potassium carbonate (88 mg, 0.634 mmol) and the reaction mixture was stirred at ambient temperature for 20 min. LCMS analysis indicated completion of the reaction. . The reaction mixture was diluted with water and extracted with dichloromethane (x 2). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated to provide the title compound as a foam, 271 mg, 0.516 mmol, 97%.

3-(4-Chloro-phenyl)-7-(2-hydroxyethylamino)-8-iodo-2-isopropyl-3H-quinazolin-4-one



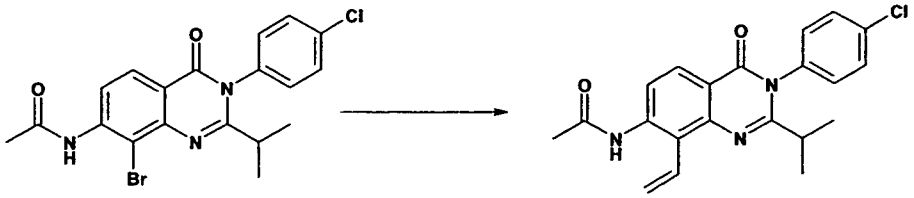
To a solution of N-[3-(4-Chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-N-(2-hydroxyethyl)acetamide (135 mg, 0.257 mmol) in methanol (2 ml) was added %M potassium hydroxide solution (1 ml). the reaction mixture was stirred at ambient temperature for 10 min and then heated to 50 °C on an oil bath for 20 min. TLC and LCMS analysis indicated complete conversion. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ethyl axcetate (x 2). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated to give a white solid. Purification by automated gradient elution flash chromatography (eluent hexane to ethyl acetate) provided the title compound as a white solid, 98 mg, 0.203 mmol, 79%.

N-[8-Bromo-3-(4-chloro-phenyl)-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acrylamide



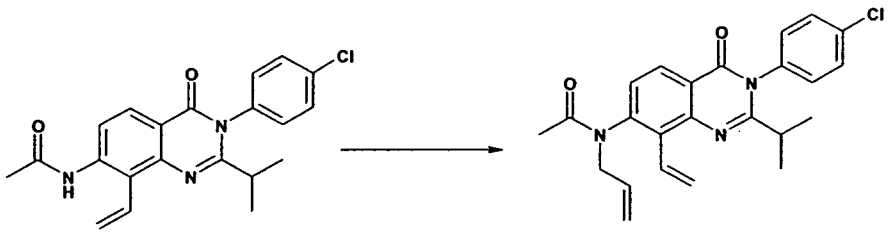
To a solution of 7-Amino-8-bromo-3-(4-chloro-phenyl)-2-isopropyl-3H-quinazolin-4-one (60 mg, 0.153 mmol) in dichloromethane in a microwave vial was added triethylamine (0.032 ml, 0.229 mmol) followed by acryloyl chloride (0.014 ml, 0.168 mmol). The vial was sealed with a crimp cap and the mixture was heated to 150 °C for 3000 s under microwave irradiation. TLC and LCMS analysis indicated complete conversion. The reaction mixture was evaporated and the residue was divided between water and dichloromethane. The organic phase was dried over anhydrous sodium sulfate and evaporated to give a yellow oil. Purification by automated gradient elution flash chromatography (eluent hexane to hexane/ethyl acetate 7/3) provided the title compound as a yellow solid, 57 mg, 0.127 mmol, 84%.

N-[3-(4-Chlorophenyl)-2-isopropyl-4-oxo-8-vinyl-3,4-dihydro-quinazolin-7-yl]-acetamide



To a suspension of N-[8-Bromo-3-(4-chloro-phenyl)-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acetamide (250 mg, 0.573 mmol) in toluene/THF 2/1 (6 ml) in a microwave vial was added tributyl(vinyl)tin (0.184 ml, 0.629 mmol) and (tetrakistriphenylphosphine)palladium(0) (66 mg, 0.057 mmol). The vial was sealed with a crimp cap and the mixture was heated to 120 °C for 1 h under microwave irradiation. TLC analysis indicated starting material remained. THF (1 ml) was added to the vial, which was re-sealed and heated to 150 °C for 1 h under microwave irradiation. TLC showed completion of the reaction. The reaction mixture was filtered through Celite, washing with methanol. The solution was evaoporated and the residue was purified by automated gradient elution flash chromatography (silica 12 g, eluent hexane (+2% triethylamine) to hexane (+2% triethylamine)/ethyl acetate 1/1) to provide the title compound as a white solid, 159 mg, 0.414 mmol, 72%.

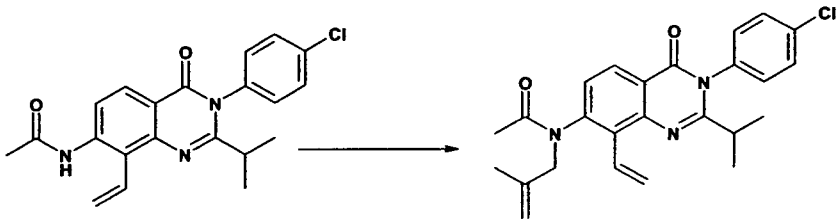
N-Allyl-N-[3-(4-chlorophenyl)-2-isopropyl-4-oxo-8-vinyl-3,4-dihydroquinazolin-7-yl]-acetamide



To a solution of of N-[3-(4-Chlorophenyl)-2-isopropyl-4-oxo-8-vinyl-3,4-dihydroquinazolin-7-yl]-acetamide (155 mg, 0.404 mmol) in DMF (3 ml) was added allyl bromide (0.037 ml, 0.42 mmol) and cesium carbonate (270 mg, 0.82 mmol). The suspension was stirred for 1 h at ambient temperature then heated to 60 °C (external temperature) in an oil bath. TLC showed completion of the reaction. The mixture was diluted with water and ethyl acetate and the aqueous phase was extracted with ethyl

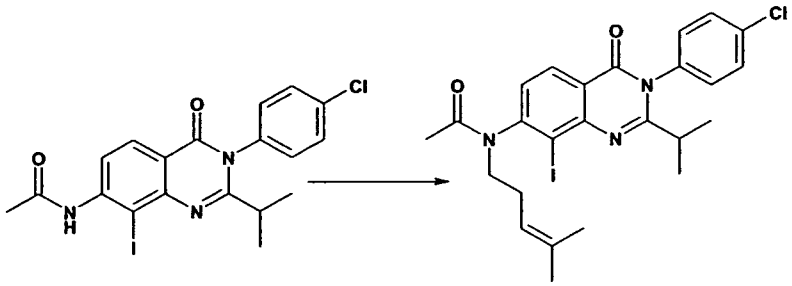
acetate (x 2). The combined organic phases were dried over anhydrous sodium sulfate and evaporated. The residue was purified by automated gradient elution flash chromatography (silica 12 g, eluent hexane to hexane/ethyl acetate 1/1) to provide the title compound as a white foam, 156 mg, 0.37 mmol, 91%.

N-[3-(4-Chloro-phenyl)-2-isopropyl-4-oxo-8-vinyl-3,4-dihydro-quinazolin-7-yl]-N-(2-methyl-allyl)-acetamide



The title compound was prepared in an analogous manner to N-Allyl-N-[3-(4-chlorophenyl)-2-isopropyl-4-oxo-8-vinyl-3,4-dihydroquinazolin-7-yl] acetamide using 3-bromo-2-methylpropene instead of allyl bromide. Yield 89%.

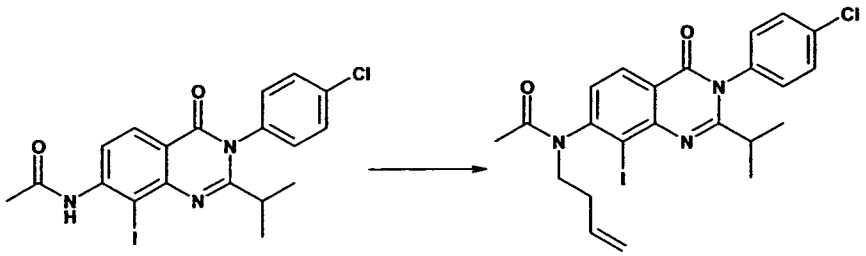
N-[3-(4-Chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-N-(4methylpent-3-enyl)acetamide



To a solution of N-[3-(4-Chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acetamide (150 mg, 0.312 mmol) in DMF (2 ml) in a microwave vial was added cesium carbonate (203 mg, 0.624 mmol) and 5-bromo-2-methyl-2-pentene (0.046 ml, 0.343 mmol). The vial was sealed with a crimp cap and the mixture was heated to 80 °C for 20 min under microwave irradiation. Additional 5-bromo-2-methyl-2-pentene (0.046 ml, 0.343 mmol) was added and the mixture was heated to 80 °C for 1 h under microwave irradiation. TLC and LCMS analysis indicated complete conversion. The reaction mixture was diluted with water, extracted with ethyl acetate (x 3) and the combined organic extracts were dried over anhydrous sodium sulfate, and evaporated. The residue was purified by automated gradient elution flash chromatography (eluent hexane to 15% ethyl acetate in

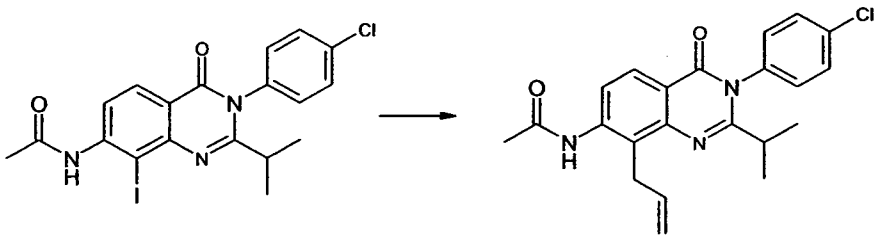
hexane) to provide the title compound as a colourless oil (136 mg, 0.241 mmol, 77%).

N-But-3-enyl-N-[3-(4-chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acetamide



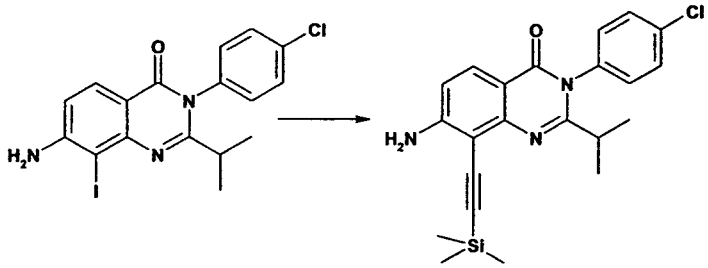
The title compound was prepared in an analogous manner to **N-[3-(4-Chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-N-(4methylpent-3-enyl)acetamide** using 4-bromobutene instead of 5-bromo-2-methyl-2-pentene. Purification by automated gradient elution flash chromatography (eluent hexane to 15% ethyl acetate in hexane) provided the title compound as a clear oil, 61%.

N-[8-Allyl-3-(4-chlorophenyl)-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acetamide



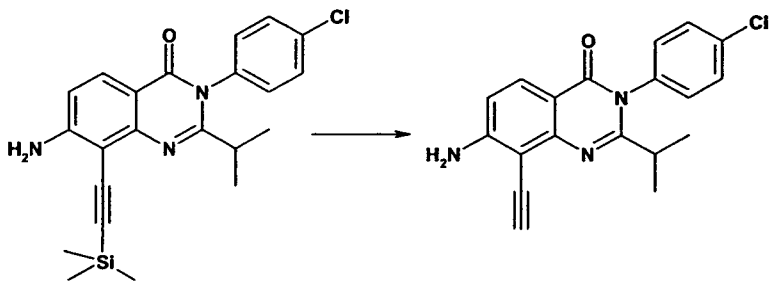
To a solution of N-[3-(4-Chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acetamide (0.2g, 0.447mmole) and $Pd(PPh_3)_4$ (0.077g, 0.067mmole) in toluene(5ml) was added allyltributyltin (0.17ml, 0.5mmole). The resulting mixture was heated in the microwave for 1hr at 140°C. The mixture was cooled down to room temperature, filtered through celite and the pad washed with EtOAc. The filtrate was washed with HCl (2M), the organic phase was dried over MgSO4 (anhydrous) and concentrated. The crude material was purified by flash chromatography(10% EtOAc/cyclohexane) to give 0.1g (62%) of N-(8-Allyl-3-(4-chlorophenyl)-2-isopropyl-4-oxo-3-phenyl-3,4-dihydro-quinazolin-7-yl)-acetamide.

7-Amino-3-(4-chloro-phenyl)-2-isopropyl-8-trimethylsilanylethynyl-3H-quinazolin-4-one



A mixture of 7-Amino-3-(4-chloro-phenyl)-8-iodo-2-isopropyl-3H-quinazolin-4-one (100 mg, 0.229 mmol), (tetrakistriphenylphosphine)palladium(0) (52 mg, 0.044 mmol), trimethylsilylacetylene (0.162 ml, 1.14 mmol), triethylamine (0.158 ml, 1.14 mmol), copper(I) iodide (18.4 mg, 0.088 mmol) and DMF was sealed in a microwave vial with a crimp cap. The reaction mixture was heated to 60 °C for 1.5 h under microwave irradiation. The mixture was evaporated and the residue was purified by automated gradient elution flash chromatography (eluent hexane to ethyl acetate) to provide the title compound (55 mg, 0.134 mmol, 59%).

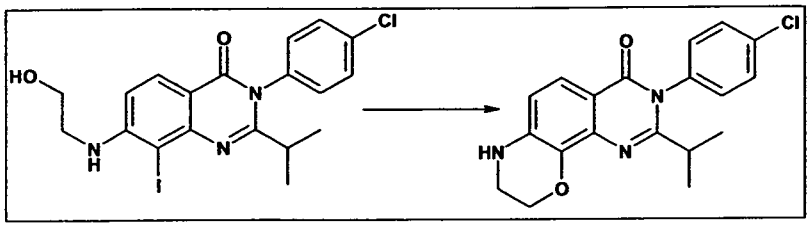
7-Amino-3-(4-chloro-phenyl)-8-ethynyl-2-isopropyl-3H-quinazolin-4-one



To a solution of 7-Amino-3-(4-chloro-phenyl)-2-isopropyl-8-trimethylsilanylethynyl-3H-quinazolin-4-one (90 mg, 0.22 mmol) in THF (8 ml) was added tetrabutylammonium fluoride (1 M in THF, 0.247 ml, 0.247 mmol). The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was partitioned between water/ethyl acetate and the aqueous layer was extracted with ethyl acetate. Evaporation gave the title compound (74 mg, 0.219 mmol, 100%), which was used without further purification.

EXAMPLE 1

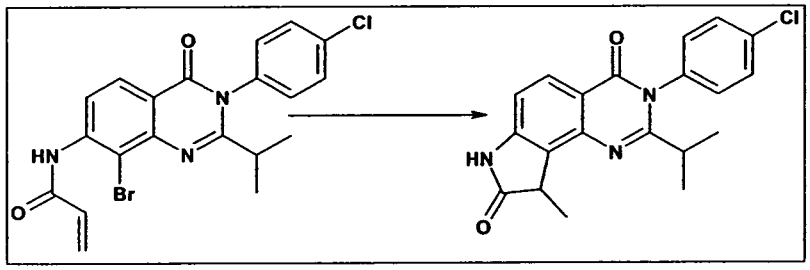
7-(4-Chloro-phenyl)-6-isopropyl-2,3-dihydro-1H,7H-4-oxa-1,5,7-triazaphenanthren-8-one



To an oven-dried microwave vial was added 3-(4-Chloro-phenyl)-7-(2-hydroxyethylamino)-8-iodo-2-isopropyl-3H-quinazolin-4-one (70 mg, 0.145 mmol), cesium carbonate (94 mg, 0.290 mmol), copper(I) iodide (27.6 mg, 0.145 mmol) and acetonitrile. The vial was sealed with a crimp cap and the mixture was heated to 150 °C for 5000 s under microwave irradiation. TLC and LCMS analysis indicated complete conversion. The reaction mixture was partitioned between water and ethylacetate. The organic phase was washed with water, dried over anhydrous sodium sulfate and evaporated to give a dark oil. Purification by automated preparative hplc provided the title compound as a white solid, 14 mg, 0.039 mmol, 27%. %). ^{1}H nmr δ_H (400 MHz, $CDCl_3$) 7.69 (1 H, d), 7.50 (2 H, d), 7.19 (2 H, d), 6.69 (1 H, d), 4.45 (2 H, t), 4.27 (1 H, brs), 3.57 (2 H, t), 2.67 (1 H, m), 1.23 (6 H, d).

EXAMPLE 2

3-(4-Chloro-phenyl)-2-isopropyl-9-methyl-7,9-dihydro-3H-pyrrolo[2,3-h]quinazoline-4,8-dione

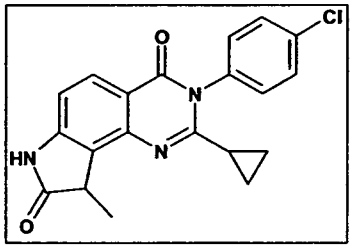


To a solution of N-[8-Bromo-3-(4-chloro-phenyl)-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acrylamide (41 mg, 0.092 mmol) in acetonitrile (4.5 ml) in a microwave vial was added (tetrakistriphenylphosphine)palladium(0) (10 mg, 0.0086 mmol), followed by triethylamine (0.064 ml, 0.46 mmol). The vial was sealed with a crimp cap and the mixture was heated to 150 °C for 5000 s under microwave irradiation. TLC analysis indicated complete conversion. The reaction mixture was

filtered through Celite. The filtrate was evaoporated and the yellow residue was purified by automated gradient elution flash chromatography (silica 12 g, eluent hexane to hexane/ethyl acetate 7/3) to provide the title compound as a yellow solid, 10.5 mg, 0.028 mmol, 31%). ^{1}H nmr δ_H (400 MHz, $CDCl_3$) 8.18 (1 H, d), 7.53 (2 H, d), 7.21 (2 H, d), 7.01 (1 H, d), 3.85 (1 H, q), 2.65 (1 H, m), 1.76 (3 H, d), 1.23 (6 H, m).

EXAMPLE 3

3-(4-Chloro-phenyl)-2-cyclopropyl-9-methyl-7,9-dihydro-3H-pyrrolo[2,3-h]quinazoline-4,8-dione

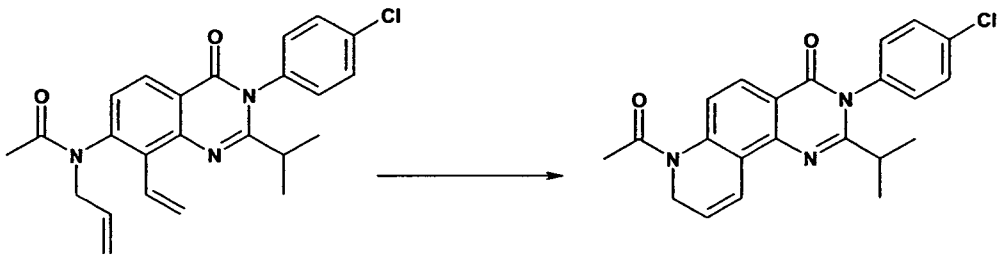


Prepared analogously to Example 2.

MH+ 366. HPLC ret time 4.6 min. 1H NMR (400 MHz, CDCl3): 8.18 (d, 1H), 8.16 (s,1H), 7.5 (d, 2H), 7.3 (d, 2H), 6.9 (d, J= 8.3Hz, 1H), 1.7 (d, 3H), 1.4 (t, 2H), 1.3 (m, 1H), 1.2 (m,1H), 0.9 (t, 2H).

EXAMPLE 4

7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-7,8-dihydro-3H-pyrido[2,3-h]quinazolin-4-one

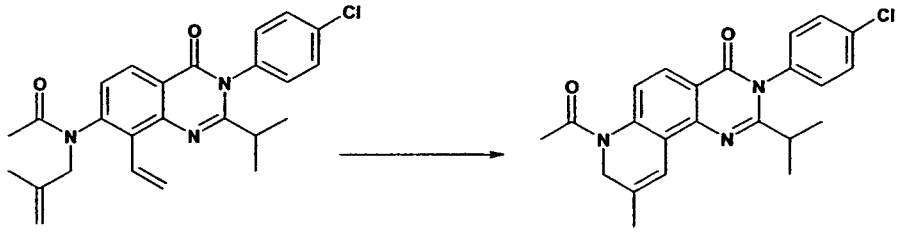


To a solution of N-Allyl-N-[3-(4-chlorophenyl)-2-isopropyl-4-oxo-8-vinyl-3,4-dihydroquinazolin-7-yl]-acetamide (62 mg, 0.147 mmol) in DCM (5 ml) in a

microwave vial was added Grubbs second generation ring closing metathesis catalyst (10.6 mg, 0.012 mmol). The vial was sealed with a crimp cap and the mixture was heated to 60 °C for 1 h under microwave irradiation. TLC showed completion of the reaction. The mixture was evaporated and the residue was purified by automated gradient elution flash chromatography (silica 4 g, eluent hexane to hexane/ethyl acetate 3/2) to provide the title compound as a colourless foam, 55.5 mg, 0.141 mmol, 96%.

EXAMPLE 5

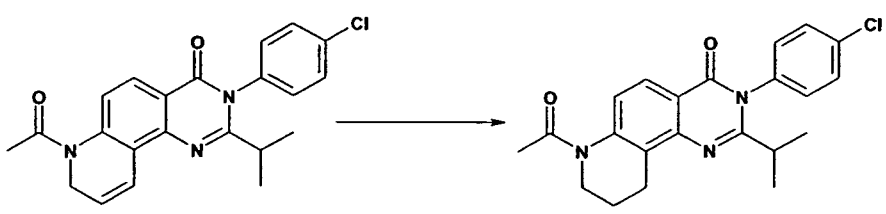
7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methyl-7,8-dihydro-3H-pyrido[2,3-h]quinazolin-4-one



The title compound was prepared in an analogous way to 7-acetyl-3-(4-chloro-phenyl)-2-isopropyl-7,8-dihydro-3H-pyrido[2,3-h]quinazolin-4-one using N-[3-(4-chloro-phenyl)-2-isopropyl-4-oxo-8-vinyl-3,4-dihydro-quinazolin-7-yl]-N-(2-methyl-allyl) acetamide instead of N-allyl-N-[3-(4-chlorophenyl)-2-isopropyl-4-oxo-8-vinyl-3,4-dihydroquinazolin-7-yl] acetamide, increasing the catalytic loading to 20 mol% and extending the reaction time to 17 h. Yield 42%.

EXAMPLE 6

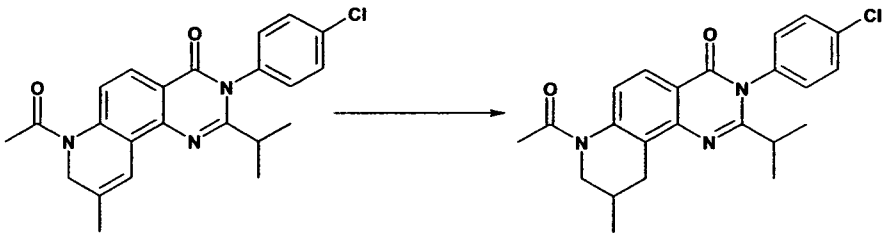
7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one



To a solution of 7-Acetyl-3-(4-chlorophenyl)-2-isopropyl-7,8-dihydro-3H-pyrido[2,3-h]quinazolin-4-one (55 mg, 0.139 mmol) in glacial acetic acid (4 ml) was added a catalytic amount of palladium on activated charcoal (10% Pd-C) and the mixture was stirred under an atmosphere of hydrogen (balloon) for 2 h. LCMS analysis showed completion of the reaction. The suspension was filtered through Celite and evaporated to yield the title compound as a pale yellow oil (58.1 mg, >100%), which was used without purification.

EXAMPLE 7

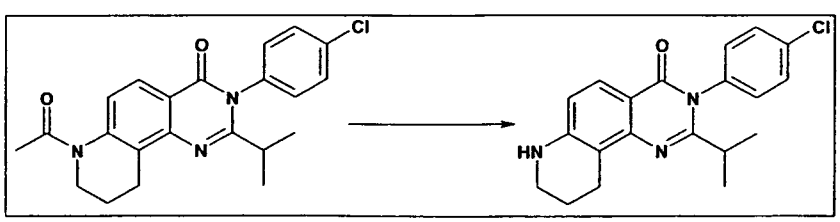
7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one



The title compound was prepared in an analogous way to 7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one replacing 7-acetyl-3-(4-chlorophenyl)-2-isopropyl-7,8-dihydro-3H-pyrido[2,3-h]quinazolin-4-one with 7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methyl-7,8-dihydro-3H-pyrido[2,3-h]quinazolin-4-one. Yield 89%.

EXAMPLE 8

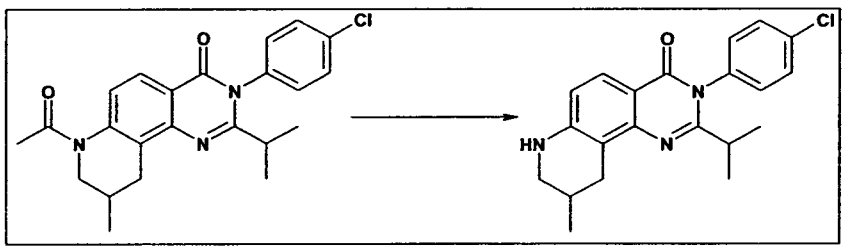
3-(4-Chloro-phenyl)-2-isopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3h]quinazolin-4-one



To a solution of 7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one (29 mg, 0.073 mmol) in methanol (2 ml) in a microwave vial was added 2 M HCl (1 ml). The vial was sealed with a crimp cap and the mixture was heated to 100 °C for 0.5 h under microwave irradiation. TLC showed completion of the reaction. The reaction mixture was basified to pH 9 by addition of saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (x 3). The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The residue was purified by automated gradient elution flash chromatography (silica 4 g, eluent hexane to hexane/ethyl acetate 3/2) to provide the title compound as a white crystalline solid, 11.9 mg, 0.034 mmol, 46%. ^{1}H nmr δ_H (400 MHz, $CDCl_3$) 7.86 (1 H, d), 7.49 (2 H, d), 7.17 (2 H, d), 6.55 (1 H, d), 4.40 (1 H, brs), 3.40 (2 H, t), 3.12 (2 H, t), 2.61 (1 H, m), 2.00 (2 H, m), 1.19 (6 H, d).

EXAMPLE 9

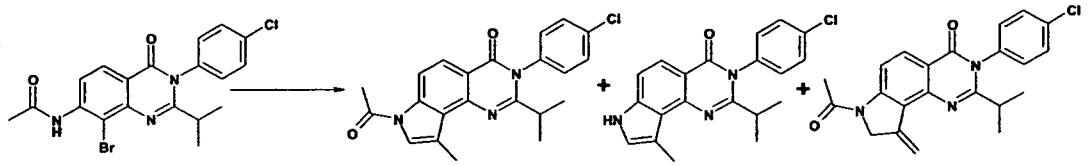
3-(4-Chloro-phenyl)-2-isopropyl-9-methyl-7,8,9,10-tetrahydro-3H-pyrido [2,3-h]quinazolin-4-one



The title compound was prepared in an analogous way to 3-(4-Chloro-phenyl)-2-isopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3h]quinazolin-4-one replacing 7-acetyl-3-(4-chloro-phenyl)-2-isopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one with 7-acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one. Yield 50%. ^{1}H nmr δ_H (400 MHz, $CDCl_3$) 7.86 (1 H, d), 7.48 (2 H, d), 7.17 (2 H, d), 6.56 (1 H, d), 4.42 (1 H, brs), 3.44 (1 H, dd), 3.37 (1 H, brd), 2.98 (1 H, t), 2.61 (1 H, m), 2.48 (1 H, dd), 2.08 (brm), 1.20 (3 H, d), 1.14 (3 H, d).

EXAMPLE 10

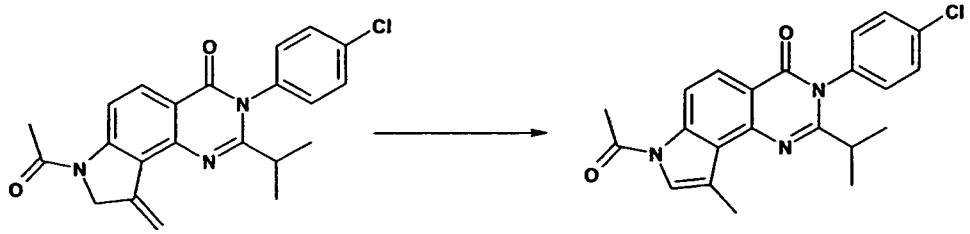
7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one, 3-(4-Chloro-phenyl)-2-isopropyl-9-methyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one and 7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methylene-8,9-dihydro-3H,7H-pyrrolo[2,3-h]quinazolin-4-one



To a solution of N-[8-Bromo-3-(4-chloro-phenyl)-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acetamide (92 mg, 0.211 mmol) in DMF (3 ml) in a microwave vial was added cesium carbonate (140 mg, 0.43 mmol) and allyl bromide (0.02 ml, 0.231 mmol). The reaction mixture was stirred at ambient temperature overnight. TLC and LCMS analysis indicated complete loss of starting material. (Tetrakistriphenylphosphine)palladium(0) (40 mg, 0.035 mmol) was added, the vial was re-sealed with a crimp cap and the mixture was heated to 100 °C for 20 min under microwave irradiation. LCMS analysis indicated complete loss of the N-allyl intermediate. The reaction mixture was evaporated and the residue was divided between ethyl acetate/water. The aqueous layer was extracted with ethyl acetate (x 2) and the combined organic extracts were dried over anhydrous sodium sulfate and evaporated. The residue was purified by automated gradient elution flash chromatography (silica 12 g, eluent hexane to hexane/ethyl acetate 1/1) to provide the title compounds: **7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one** (eluting first, 8.8 mg, 0.022 mmol, 11%); **3-(4-Chloro-phenyl)-2-isopropyl-9-methyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one** (eluting second, 6 mg, 0.015 mmol, 8%) and **7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methylene-8,9-dihydro-3H,7H-pyrrolo[2,3h]quinazolin-4-one** (eluting third, 48 mg, 0.122 mmol, 58%). Total recovery: 77%.

EXAMPLE 11

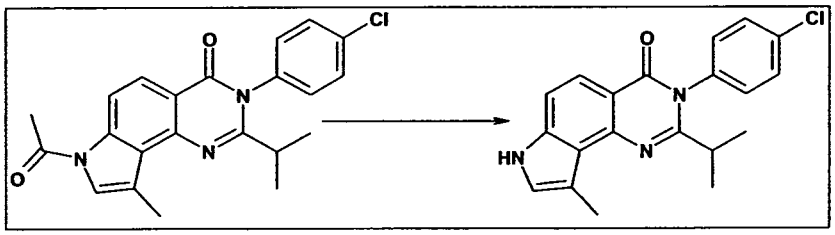
7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methyl-3H,7H-pyrrolo[2,3h]quinazolin-4-one



To a solution of **7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methylene-8,9-dihydro-3H,7H-pyrrolo[2,3h]quinazolin-4-one** (48 mg, 0.122 mmol) in DCM (2 ml) was added camphorsulfonic acid (29 mg, 0.122 mmol). The reaction mixture was stirred for 20 h at room temperature. LCMS showed complete loss of starting material. The reaction mixture was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (x 2) and the combined organic extracts were dried over anhydrous sodium sulfate, and evaporated to give the title compound (48 mg, 0.122 mmol, 100%), which was used without purification.

EXAMPLE 12

3-(4-Chloro-phenyl)-2-isopropyl-9-methyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one

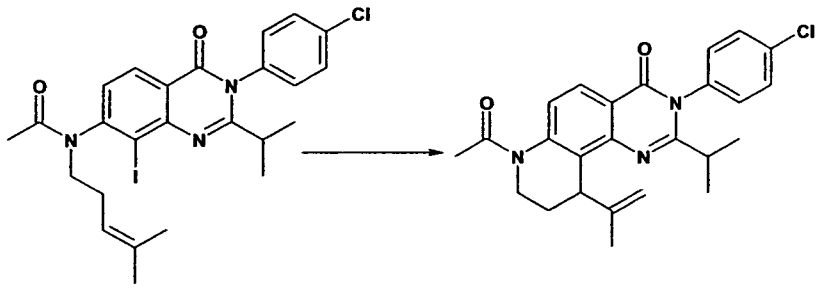


To a solution of of 7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-9-methylene-8,9-dihydro-3H,7H-pyrrolo[2,3h]quinazolin-4-one (48 mg, 0.122 mmol) in methanol/water 2/1 (3 ml) in a microwave vial was added potassium carbonate (150 mg, 1.087 mmol). The vial was sealed with a crimp cap and the mixture was heated to 120 °C for 0.5 h under microwave irradiation. TLC analysis showed completion of the reaction. The reaction mixture was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (x 2) and the combined organic extracts were dried over anhydrous sodium sulfate, and evaporated. The residue was purified by automated gradient elution flash chromatography (silica 4 g, eluent hexane to hexane/ethyl acetate 1/1) to provide the title compound as a yellow solid (25.4 mg, 0.072 mmol,

59%). ^{1}H nmr δ_H (400 MHz, $CDCl_3$) 8.33 (1 H, brs), 8.00 (1 H, d), 7.53 (2 H, d), 7.39 (1 H, d), 7.23 (2 H, d), 7.06 (1 H, m), 2.76 (3 H, s) 2.71 (1 H, m), 1.27 (6 H, d).

EXAMPLE 13

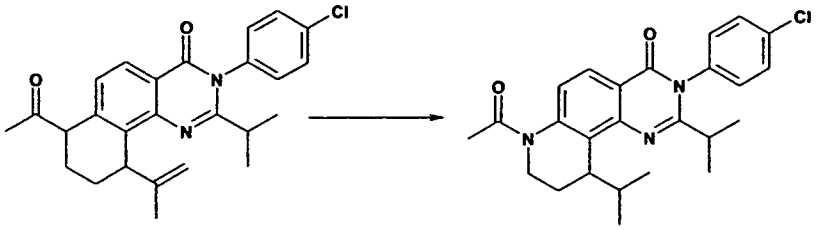
7-Acetyl-3-(4-chloro-phenyl)-10-isopropenyl-2-isopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one



To an oven-dried, microwave vial was added N-[3-(4-Chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-N-(4methylpent-3-enyl)acetamide (61 mg, 0.108 mmol), (tetrakistriphenylphosphine)palladium(0) (25 mg, 0.022mmol), cesium carbonate (176 mg, 0.541 mmol) and DMF (2.5 ml). The vial flushed with nitrogen, sealed with a crimp cap and the mixture was heated to 120 °C for 1 h under microwave irradiation. TLC and LCMS analysis indicated completion. The reaction mixture was poured into water, extracted with ethyl acetate (x 2) and the combined organic extracts were dried over anhydrous sodium sulfate, and evaporated. The residue was purified by automated gradient elution flash chromatography (eluent hexane to 15% ethyl acetate in hexane) to provide the title compound as a clear, pale yellow oil (46 mg, 0.105 mmol, 98%).

EXAMPLE 14

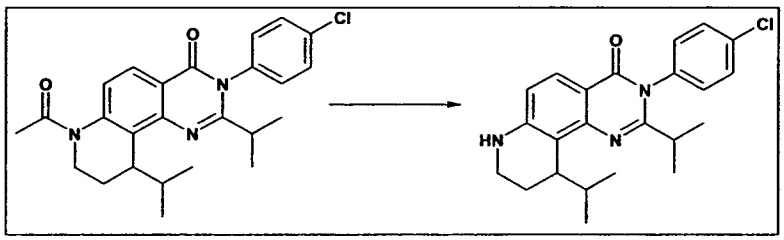
7-Acetyl-3-(4-chloro-phenyl)-2,10-diisopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one



To a solution of 7-Acetyl-3-(4-chloro-phenyl)-10-isopropenyl-2-isopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one (44 mg, 0.101 mmol) in absolute ethanol/glacial acetic acid 1/1 (3 ml) was added a catalytic amount of palladium on activated charcoal (10% Pd-C, 10 mg) and the mixture was stirred under an atmosphere of hydrogen (balloon) for 5 h. LCMS analysis showed completion of the reaction. The suspension was filtered through Celite and the filtrate was neutralized with saturated aqueous sodium hydrogen carbonate. The aqueous solution was extracted with dichloromethane and the organic extracts were evaporated. The residue was purified by automated gradient elution flash chromatography (eluent hexane to 20% ethyl acetate in hexane) to provide the title compound as a clear oil (37 mg, 0.084 mmol, 84%).

EXAMPLE 15

3-(4-Chloro-phenyl)-2,10-diisopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one

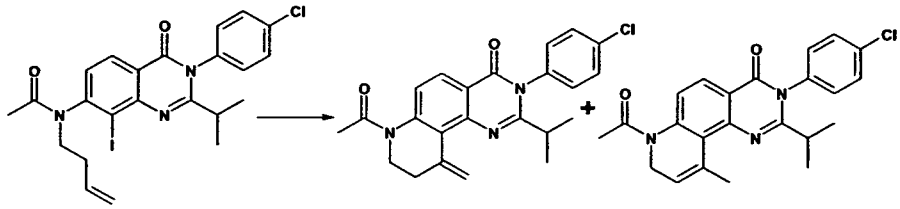


To a solution 7-Acetyl-3-(4-chloro-phenyl)-2,10-diisopropyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one (30 mg, 0.068 mmol) in methanol (1 ml) in a microwave vial was added aqueous potassium hydroxide solution (1 M, 1 ml). The vial was sealed with a crimp cap and the mixture was heated to 100 °C for 10 min under microwave irradiation. TLC and LCMS analysis indicated completion. The reaction mixture was diluted with dilute hydrochloric acid and extracted with ethyl acetate (x 2). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous sodium sulfate and evaporated to give a clear oil (24 mg, 0.060 mmol, 89%). ^{1}H nmr δ_H (400 MHz, $CDCl_3$) 7.88 (1 H,

d), 7.48 (2 H, m), 7.22 (1 H, m), 7.16 (1 H, m), 6.55 (1 H, d), 4.45 (1 H, brs), 3.61 (1 H, m), 3.44 (2 H, m), 2.62 (1 H, m), 2.14 (1 H, dd), 1.93 (1H, m), 1.69 (1 H, m), 1.19 (6 H, m), 1.04 (3 H, d), 0.90 (3 H, d).

EXAMPLE 16

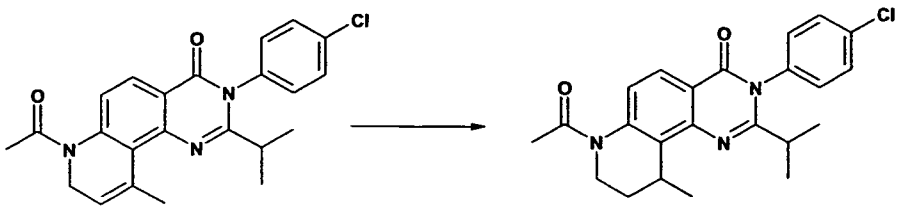
7-Acetyl-3-(4-chlorophenyl)-2-isopropyl-10-methylene-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one and 7-Acetyl-3-(4-chlorophenyl)-2-isopropyl-10-methyl-7,8-dihydro-3H-pyrido[2,3-h]quinazolin-4-one



To an oven-dried, microwave vial was added but-3-enyl-N-[3-(4-chloro-phenyl)-8-iodo-2-isopropyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-acetamide (350 mg, 0.654 mmol), DMF (5 ml). (tetrakistriphenylphosphine)palladium(0) (151 mg, 0.131 mmol) and cesium carbonate (1.1 g, 3.4 mmol). The vial was flushed with nitrogen, sealed with a crimp cap and the mixture was heated to 100 °C for 1 h under microwave irradiation. TLC and LCMS analysis indicated completion. The reaction mixture was filtered through Celite and evaporated. Ethyl acetate/water was added to the residue and the organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give a dark oil. The residue was purified by automated gradient elution flash chromatography (eluent hexane to 25% ethyl acetate in hexane) to provide the title isomeric compounds: **7-Acetyl-3-(4-chlorophenyl)-2-isopropyl-10-methylene-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one** (108 mg, 0.265 mmol, 41%); and **7-Acetyl-3-(4-chlorophenyl)-2-isopropyl-10-methyl-7,8-dihydro-3H-pyrido[2,3-h]quinazolin-4-one** (138 mg, 0.338 mmol, 52%). Total recovery: 93%.

EXAMPLE 17

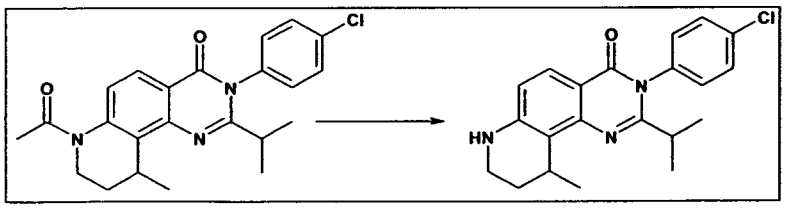
7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-10-methyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one



To a solution of 7-Acetyl-3-(4-chlorophenyl)-2-isopropyl-10-methyl-7,8-dihydro-3H-pyrido[2,3-h]quinazolin-4-one (100 mg, 0.246 mmol) in absolute ethanol/glacial acetic acid 1/10 (5.5 ml) was added a catalytic amount of palladium on activated charcoal (10% Pd-C, 10 mg) and the mixture was stirred under an atmosphere of hydrogen (balloon) for 20 h. LCMS analysis showed completion of the reaction. The suspension was filtered through Celite and evaporated. The residue was purified by automated gradient elution flash chromatography (eluent hexane to 30% ethyl acetate in hexane) to provide the title compound as a clear oil (89 mg, 0.218 mmol, 89%).

EXAMPLE 18

3-(4-Chloro-phenyl)-2-isopropyl-10-methyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one

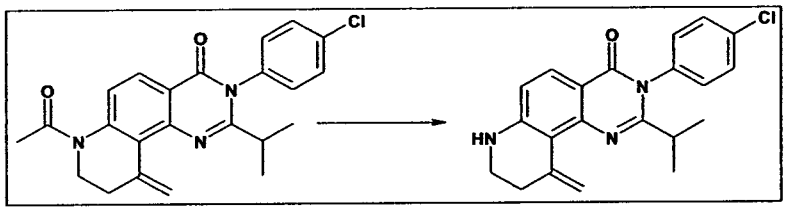


To a solution of 7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-10-methyl-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one (84.5 mg, 0.207 mmol) in methanol (5 ml) in a microwave vial was added aqueous potassium hydroxide solution (5 M, 1 ml). The vial was sealed with a crimp cap and the mixture was heated to 100 °C for 10 min under microwave irradiation. TLC and LCMS analysis indicated completion. The reaction mixture was diluted with water and extracted with ethyl acetate (x 2). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated. The residue was purified by automated gradient elution flash chromatography (eluent hexane to 20% ethyl acetate in hexane) to provide the title

compound as a white solid (60 mg, 0.163 mmol, 79%). %). ^{1}H nmr δ_H (400 MHz, $CDCl_3$) 7.86 (1 H, d), 7.48 (2 H, d), 7.18 (2 H, m), 6.54 (1 H, d), 4.49 (1 H, brs), 3.83 (1 H, m), 3.48 (1 H, m), 3.36 (1 H, m), 2.61 (1 H, m), 1.93 (1 H, m), 1.82 (1 H, m), 1.33 (3 H, d), 1.21 (6 H, m).

EXAMPLE 19

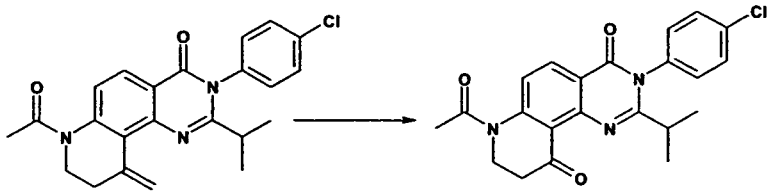
3-(4-Chloro-phenyl)-2-isopropyl-10-methylene-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one



To a solution of 7-Acetyl-3-(4-chlorophenyl)-2-isopropyl-10-methylene-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one (60mg, 0.147 mmol) in methanol (3 ml) in a microwave vial was added aqueous potassium hydroxide solution (5 M, 1 ml). The vial was sealed with a crimp cap and the mixture was heated to 100 °C for 10 min under microwave irradiation. TLC and LCMS analysis indicated completion. The reaction mixture was acidified to pH 6-7 with hydrochloric acid (2M) and extracted with ethyl acetate (x 2). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated. The residue was purified by automated gradient elution flash chromatography (eluent hexane to 20% ethyl acetate in hexane) to provide the title compound as a white solid (35 mg, 0.096 mmol, 65%). %). ^{1}H nmr δ_H (400 MHz, $CDCl_3$) 7.90 (1 H, d), 7.49 (2 H, d), 7.19 (2 H, d), 6.63 (1 H, d), 6.55 (1 H, d), 5.32 (1 H, brm), 4.63 (1 h, brs), 3.50 (2 H, brt), 2.66 (3 H, overlapping m), 1.20 (6 H, d).

EXAMPLE 20

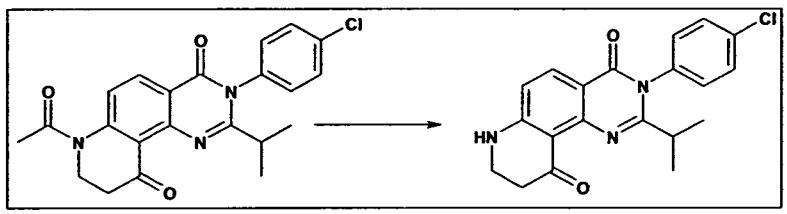
7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-8,9-dihydro-3H,7H-pyrido[2,3-h]quinazoline-4,10-dione



A solution of 7-Acetyl-3-(4-chlorophenyl)-2-isopropyl-10-methylene-7,8,9,10-tetrahydro-3H-pyrido[2,3-h]quinazolin-4-one (85 mg, 0.208 mmol) in methanol/dichloromethane 2/1 (5 ml) was cooled to -78 °C and a steady stream of ozone was bubbled into the reaction mixture over 0.5 h. The reaction mixture was allowed to warm to -20 °C whilst being purged with a steady stream of argon. The solution was then cooled to -78 °C and dimethyl sulfide (3 drops) was added. The stirred solution was allowed to reach ambient temperature overnight and then evaporated. The residue was purified by automated gradient elution flash chromatography (eluent hexane to 80% ethyl acetate in hexane) to provide the title compound as a white solid (38 mg, 0.093 mmol, 44%).

EXAMPLE 21

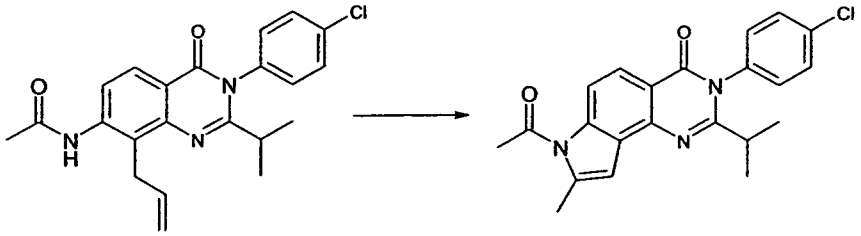
3-(4-Chloro-phenyl)-2-isopropyl-8,9-dihydro-3H,7H-pyrido[2,3-h]quinazoline-4,10-dione



To a solution of 7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-8,9-dihydro-3H,7H-pyrido[2,3-h]quinazoline-4,10-dione (30mg, 0.073 mmol) in methanol (4 ml) was added aqueous potassium hydroxide solution (5 M, 1 ml). After 2 min, TLC and LCMS analysis indicated completion. The reaction mixture was diluted with water and extracted with ethyl acetate (x 2). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated. The residue was purified by automated gradient elution flash chromatography (eluent hexane to 70% ethyl acetate) to provide the title compound as a white solid (11.9 mg, 0.032 mmol, 44%). ^{1}H nmr δ_H (400 MHz, $CDCl_3$) 8.07 (1 H, d), 7.51 (2 H, d), 7.17 (2 H, d), 6.66 (1 H, d), 5.12 (1 H, brs), 3.70 (2 H, brm), 2.81 (2 H, t), 2.66 (1 H, m), 1.26 (6 H, d).

EXAMPLE 22

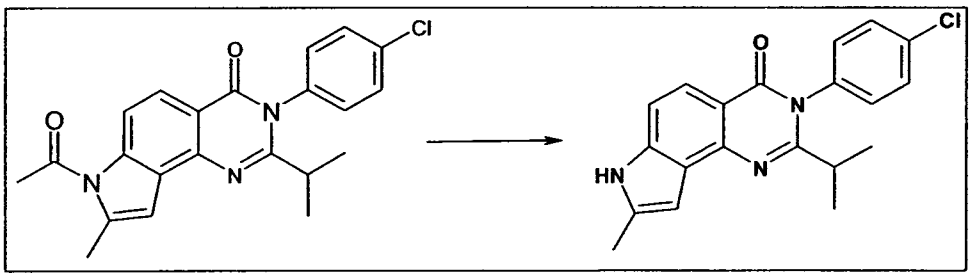
7-Acetyl-3-(4-chlorophenyl)-2-isopropyl-8-methyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one



To a solution of N-(8-Allyl-2-isopropyl-4-oxo-3-phenyl-3,4-dihydro-quinazolin-7-yl)-acetamide(**2**)(0.02g, 0.05mmole) in THF(3ml) was added PdCl2(MeCN)2 (0.013g, 0.05mmole) and stirred at room temperature for 1hr. To this solution was added Et3N(0.02ml, 0.15mmole) and stirred for 2hrs. Reaction mixture was filtered through celite and washed pad with EtOAc. The filtrate was concentrated and purified by flash chromatography(10% EtOAc/cyclohexane) to give 0.01g (51%) of 7-Acetyl-3-(4-chlorophenyl)-2-isopropyl-8-methyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one.

EXAMPLE 23

3-(4-Chlorophenyl)-2-isopropyl-8-methyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one

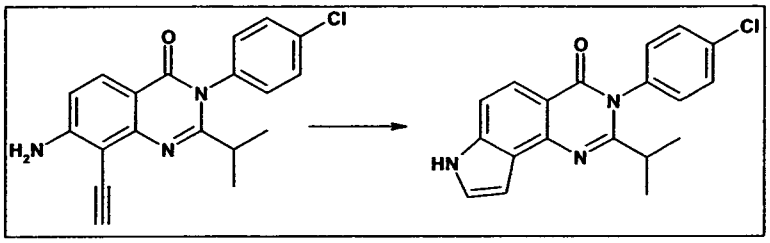


To a solution of 7-Acetyl-3-(4-chloro-phenyl)-2-isopropyl-8-methyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one(**3**)(0.02g, 0.05mmole) in MeOH(0.5m) was added 2ml of KOH (5M) and heated in the microwave at 100oC for 2hrs. Reaction mixture was diluted with H2O, extracted with EtOAc,the organic phase was dried over MgSO4 (anhydrous) and concentrated to give 0.016g (90%) of 3-(4-Chlorophenyl)-2-isopropyl-8-methyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one. MH+ = 352. HPLC

retention time = 5.7 min. δH (400MHz, $CDCl_3$) 8.28 (s, 1H), 7.9 (d,1H), 7.5 (d, 2H), 7.3 (d, 1H), 7.2 (d, 2H), 6.8 (s, 1H), 2.7 (m, 1H), 2.5 (s,3H), 1.2 (d, 6H).

EXAMPLE 24

3-(4-Chloro-phenyl)-2-isopropyl-3H,7H-pyrrolo[2,3-h]quinazolin-4-one



To a suspension of potassium hydride CAUTION PYROPHORIC (30% dispersion in mineral oil, 36 mg, 0.27 mmol) in NMP in an oven-dried, argon-flushed microwave vial was added a solution of 7-Amino-3-(4-chloro-phenyl)-8-ethynyl-2-isopropyl-3H-quinazolin-4-one (33.5 mg, 0.099 mmol) in NMP. The microwave vial was sealed with a crimp cap and the reaction mixture was stirred overnight at room temperature. LCMS analysis indicated 50% completion of the reaction. The reaction mixture was heated at 70 °C for 1 h under microwave irradiation. LCMS analysis indicated completion. The reaction mixture was diluted with water and extracted with ethyl acetate (x 2). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated.

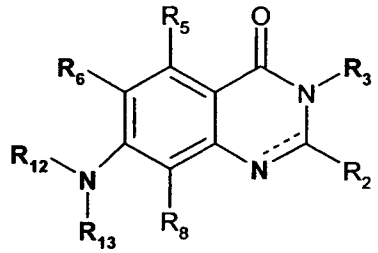
Alternative procedure: To a suspension of potassium tertiary-butoxide (36 mg, 0.32 mmol) in NMP in an oven-dried, argon-flushed microwave vial was added a solution of 7-Amino-3-(4-chloro-phenyl)-8-ethynyl-2-isopropyl-3H-quinazolin-4-one (43 mg, 0.127 mmol) in NMP. The microwave vial was sealed with a crimp cap and the reaction mixture was heated at 80 °C for 1 h under microwave irradiation. LCMS analysis indicated completion. The reaction mixture was diluted with water and extracted with ethyl acetate (x 2). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated.

The combined residues for the two procedures was purified by automated gradient elution flash chromatography (eluent 5 to 100% ethyl acetate in hexane) to provide the title compound (40 mg, 0.119 mmol, 52%). ^1H nmr δ_H (400 MHz, $CDCl_3$) 8.54 (1

H, brs), 8.04 (1 H, d), 7.52 (2 H, m), 7.47 (1 H, d), 7.33 (1 H, t), 7.23 (3 H, m), 2.72 (1 H, m), 1.26 (6 H, d).

Claims

1. A quinazolinone compound of the formula



(I)

,

wherein

---- is a single bond or a double bond;

R_2 is selected from

(a) C_1-C_8alkyl, C_3-C_6cycloalkyl, (C_1-C_6alkyl)amino or di-(C_1-C_6alkyl)amino;

or

(b) NH_2, hydroxyC_1-C_6alkylamino-, aminoC_1-C_6alkylamino, C_2-C_6alkenyl, di(trifluoromethyl)C_1-C_6alkyl, R_9-O-(C_1–C_6alkyl)- in which the alkyl chain is optionally substituted by trifluoromethyl, (NC)-C_1–C_6alkyl-, ($R_{10}R_{11}$N-)C_1–C_6alkyl-, (C_1–C_6alkyl)-SO_2-(C_1–C_6alkyl)-, wherein R_9, R_{10} and R_{11} are each independently H or C_1-C_6 alkyl; phenyl optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1–C_6alkyl, halogen-substituted C_1–C_6alkyl, hydroxy C_1–C_6alkyl, cyano or a group –(C=O)-R_{2a}, where R_{2a} is C_1–C_6alkyl; or 5, 6, or 7-membered, saturated or unsaturated, heterocyclic ring, directly attached to the quinazolinone ring or attached through -C_1–C_6 alkyl-, containing one, two, or three heteroatoms selected from N, O and S, and optionally substituted with one, two or three substitutents selected from C_1–C_6alkyl, C_1–C_6alkoxy, hydroxy, cyano, halo, $R_{10}R_{11}$N-, R_9-O-(C=O)-, -(C=O)-N-$R_{10}R_{11}$, =O and phenyl ;

R_3 is selected from

(a'):

phenyl substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_6alkyl, halogen-substituted C_1-C_6alkyl, hydroxyC_1-C_6alkyl, cyano or a group –C(=O)-R_{3a}, where R_{3a} is C_1-C_6alkyl; or

(b'):

C_1–C_6alkyl, (NC)-C_1–C_6alkyl-, R_9-O-(C_1–C_6alkyl)-, R_9-O-(C_1–C_6alkyl)-O-(C_1–C_6alkyl)-,$R_{10}R_{11}$N-(C_1–C_6alkyl)-, $R_{10}R_{11}$N-(C=O)-(C_1–C_6alkyl)-, or (C_1–C_6alkyl)-SO_2-(C_1–C_6alkyl)-, wherein R_9, R_{10} and R_{11} are each independently H or C_1-C_6 alkyl; or

unsubstituted phenyl, phenyl substituted with one or two substituents selected from -(C_1–C_6alkoxy)-, $R_{10}R_{11}$N-, $R_{10}R_{11}$N-(C_1–C_6alkyl)-, -SO_2-(C_1–C_6alkyl), R_9-O-(C=O)-, wherein R_9, R_{10} and R_{11} are as defined above, or with halo-substituted phenyl or a 5- or 6-membered saturated or unsaturated heterocyclic ring having one, two or three heteroatoms selected from N, O and S and optionally including a further substituent selected from halo, or phenyl substituted with three or four substituents selected from halo, hydroxyl, and C_1–C_6alkyl; or

a cycloalkyl ring having 3, 4, 5 or 6 carbon atoms, directly attached to the quinazolinone ring or attached through -C_1–C_6alkyl-, and which is optionally substituted with one or two substituents selected from C_1–C_6alkyl, C_1–C_6alkoxy, hydroxy, cyano, halo, $R_{10}R_{11}$N-, R_9-O-(C=O)-, -(C=O)-N-$R_{10}R_{11}$, and phenyl; or

benzyl, or phenyl(C_1–C_6alkyl)-, phenoxy-(C_1–C_6alkyl)- or phenyl(C=O)-(C_1–C_6alkyl)-, optionally substituted with one, two, or three substituents selected from C_1–C_6alkyl, C_1–C_6alkoxy, hydroxy, cyano, halo, $R_{10}R_{11}$N-, R_9-O-(C=O)-, -(C=O)-N-$R_{10}R_{11}$, and phenyl; or

a 5, 6, or 7- membered, saturated or unsaturated, heterocyclic ring, directly attached to the quinazolinone ring or attached through -C_1–C_6 alkyl-, containing one, two, or three heteroatoms selected from N, O and S, and optionally substituted with one, two or three substitutents selected from C_1–C_6alkyl, C_1–C_6alkoxy, hydroxy, cyano, halo, $R_{10}R_{11}$N-, R_9-O-(C=O)-, -(C=O)-N-$R_{10}R_{11}$, =O and phenyl; or

a 9- or 10- membered aromatic or heterocyclic fused ring, directly attached to the quinazolinone ring or attached through -C_1–C_6 alkyl-, containing zero, one, two or three heteroatoms selected from N, O and S, and optionally substituted with one, two, three or four substitutents selected from C_1–C_6alkyl, C_1–C_6alkoxy, hydroxy, cyano, halo, $R_{10}R_{11}N$-, R_9-O-(C=O)-, -(C=O)-N-$R_{10}R_{11}$, and phenyl; and

R_5 and R_6 are each independently hydrogen, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, hydroxy, hydroxy-substituted C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, cyano, -C(=O)H, phenyl, (C_3-C_6cycloalkyl)C_1-C_6alkyl, (C_3-C_6cycloalkyl)C_1-C_6alkoxy, (C_1-C_6alkoxycarbonylamino)C_1-C_6alkoxy or (C_1-C_6alkylcarbonylamino)C_1-C_6alkoxy, (amino) C_1-C_6alkoxy, (dimethylamino)C_1-C_6alkoxy, or (C_1-C_6alkoxycarbonyl) C_1-C_6alkoxy;

R12 is hydrogen, formyl, C_1-C_6alkylcarbonyl or benzyl, the phenyl group of which is optionally substituted by 1, 2 or 3 substituents, selected from the group consisting of halogen, C_1-C_6alkyl, halo-C_1-C_6alkyl, hydroxy, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, halo-C_1-C_6alkoxy, C_1-C_6alkylthio, halo-C_1-C_6alkylthio, C_1-C_6alkylsulfinyl, halo-C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, halo-C_1-C_6alkylsulfonyl, C_3-C_6cycloalkyl, C_3-C_6cycloalkyl-C_1-C_6alkyl, C_3-C_6cycloalkoxy, C_3-C_6cycloalkoxy-C_1-C_6alkyl, amino, C_1-C_6alkylamino, di-(C_1-C_6alkyl)amino, C_1-C_6alkoxycarbonylamino, cyano, formyl and C_1-C_6alkylcarbonyl, or is substituted at two adjacent carbon atoms by -O-CH_2-O- or -O-CF_2-O-; and

R13 and R8, taken together, represent, together with the three-membered moiety -N-C-C-, to which they are attached, a five-, six-, seven- or eight-membered, partially or fully unsaturated, optionally substituted, heterocyclic ring, which contains 1 ring nitrogen atom and optionally either 1 further ring nitrogen, oxygen or sulfur atom or 2 further ring nitrogen atoms, in which heterocyclic ring each ring oxygen or sulfur atom is bonded to 2 ring carbon atoms, the optional substituents of the said heterocyclic ring being selected from the group consisting of halogen, C_1-C_6alkyl, halo-C_1-C_6alkyl, hydroxy-C_1-C_6alkyl, C(O) -C_1-C_6alkyl and oxo,

in free form or in salt form.

2. The use of a quinazolinone compound of the formula

(I) as defined in claim 1, for the manufacture of a medicament for the treatment or prevention of a disease or condition, in which vanilloid receptor activation plays a role or is implicated.

3. A method for treating or preventing a disease or condition, in which vanilloid receptor activation plays a role or is implicated, comprising administering to a mammal in need thereof a therapeutically effective amount of a quinazolinone compound of the formula(I) as defined in claim 1.

4. A pharmaceutical composition comprising a compound as defined in claim 1 of the formula I, in free form or in pharmaceutically acceptable salt form, in association with a pharmaceutical carrier or diluent.

5. A compound as defined in claim 1 of the formula I, in free form or in pharmaceutically acceptable salt form, for use as a medicament.

6. A combination comprising a therapeutically effective amount of a compound as defined in claim 1 of the formula I, in free form or in pharmaceutically acceptable salt form, and a second drug substance, for simultaneous or sequential administration.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/011721

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/517 C07D471/04 C07D487/04 C07D498/04 A61P25/04

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KUMARI, T. ARUNA ET AL: "A facile synthesis of 2,3-disubstituted pyrido[2,3-h]quinazolin-4(3H)-ones" XP002424032 retrieved from STN Database accession no. 2002:132282 see compounds with rn: 433223-82-6, 433223-83-7, 433223-84-8, 433223-85-9, 433223-86-0, 433223-87-1, 433223-88-2, 433223-89-3, 433223-90-6, 433223-91-7, 433223-92-8, 433223-93-9, 433223-94-0, 433223-95-1, 433223-96-2, 433223-97-3, 433223-98-4, 433223-99-5, 433224-00-1 abstract -/--	1

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2007	26/03/2007

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

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& SYNTHETIC COMMUNICATIONS , 32(2), 235-240 CODEN: SYNCAV; ISSN: 0039-7911, 2002,	
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; REDDY, M. SATYANARAYANA ET AL: "A facile synthesis of 3-aryl-2-styryl- and 3-aryl-2-methylpyrido[2,3-h]quinazolin-4(3H)-ones" XP002424033 retrieved from STN Database accession no. 1984:455033 see compounds with rn: 91118-82-0, 91118-83-1, 91118-84-2, 91118-85-3, 91118-86-4, 91118-87-5, 91118-88-6, 91118-89-7, 91118-90-0, 91118-91-1, 91118-92-2, 91118-93-3, 91118-94-4, 91118-95-5, 91118-96-6, 91118-97-7, 91118-98-8, 91118-99-9 abstract & INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY , 22B(11), 1100-2 CODEN: IJSBDB; ISSN: 0376-4699, 1983,	1
A	WO 2005/049613 A (MERCK SHARP & DOHME [GB]; BAYLISS TRACY [GB]; HOLLINGWORTH GREGORY JOH) 2 June 2005 (2005-06-02) the whole document	1-6
A	EP 1 199 307 A1 (WELLCOME FOUND [GB]) 24 April 2002 (2002-04-24) the whole document	1-6

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/011721

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/011721

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005049613 A	02-06-2005	AU 2004290626 A1	02-06-2005
		CA 2545725 A1	02-06-2005
		EP 1687306 A1	09-08-2006
EP 1199307 A1	24-04-2002	DK 1199307 T3	14-06-2004