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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 September 2007 (27.09.2007)

PCT

(10) International Publication Number
WO 2007/109045 A1

(51) International Patent Classification:
C07D 401/04 (2006.01) *A61P 35/00* (2006.01)
C07D 401/14 (2006.01) *A61P 25/00* (2006.01)
A61K 31/506 (2006.01) *A61P 29/00* (2006.01)

(21) International Application Number:
PCT/US2007/006424

(22) International Filing Date: 14 March 2007 (14.03.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/783,175 16 March 2006 (16.03.2006) US

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

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BATT, David Bryant** [US/US]; 33 Campbell Road, Wayland, MA 01778 (US). **BEERLI, René** [CH/CH]; Kirchweg 29, CH-4102 Binningen (CH). **BOLD, Guido** [CH/CH]; Bleumatthöhe 16, CH-5073 Gipf-oberfrick (CH). **CARAVATTI, Giorgio** [CH/CH]; Fuchshagweg 28, CH-4103 Bottmingen (CH). **RAMSEY, Timothy Michael** [US/US]; 45 Ox Bow Road, Weston, MA 02493 (US).

(74) Agent: **KONZAK, Kristin, E.**; Novartis, Corporate Intellectual Property, One Health Plaza, East Hanover, NJ 07936-1080 (US).

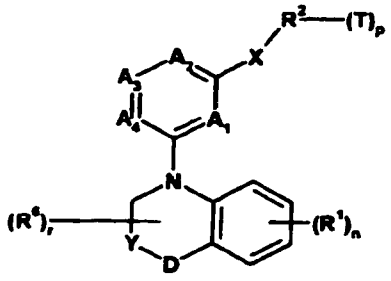
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, 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, MT, 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).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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:** HETEROCYCLIC ORGANIC COMPOUNDS FOR THE TREATMENT OF IN PARTICULAR MELANOMA



(I)

(57) **Abstract:** The present invention relates to the discovery that certain compounds inhibit, regulate and/or modulate tyrosine and serine/threonine kinase and kinase-like proteins, such as RAF kinase, a serine/threonine kinase that functions in the MAP kinase signaling pathway, and is concerned with compositions which contain these compounds, and methods of using them to treat tyrosine and serine/threonine kinase and kinase-like dependent diseases, such as angiogenesis, cancer and cardiac hypertrophy. (Formula I).

WO 2007/109045 A1

HETEROCYCLIC ORGANIC COMPOUNDS FOR THE TREATMENT OF IN PARTICULAR MELANOMA

Summary

[001] The present invention relates to the discovery that certain compounds inhibit, regulate and/or modulate tyrosine and serine/threonine kinase and kinase-like proteins, such as RAF kinase, a serine/threonine kinase that functions in the MAP kinase signaling pathway, and is concerned with compositions which contain these compounds, and methods of using them to treat tyrosine and serine/threonine kinase and kinase-like dependent diseases, such as angiogenesis, cancer and cardiac hypertrophy.

Background

[002] Cells communicate various aspects of their extracellular environment to the nucleus by using various signal transduction pathways. Many of these signals are transmitted by protein kinases which activate various factors through the transfer of phosphate groups. Disruption of signal transduction by inhibiting appropriate kinase activity can have a clinical benefit as has been demonstrated by imatinib, an inhibitor of bcr-abl kinase, which is marketed as its mesylate salt under the brand GLEEVEC (in the United States) or GLIVEC.

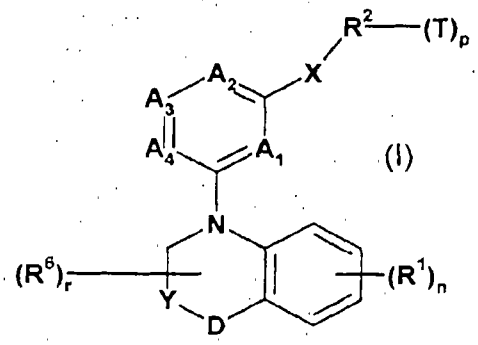
[003] The MAP kinase signaling pathway is known in the art as one of the pathways for growth factors to send their signal to proliferate from the extracellular environment to the cell nucleus. The growth factors activate transmembrane receptors located on the cell surface which in turn start a cascade whereby RAS is activated and recruits RAF kinase to the membrane where it is activated and in turn activates MEK kinase which then activates ERK kinase. Activated ERK kinase can move to the nucleus where it activates various gene transcription factors. Aberrations in this pathway can lead to altered gene transcription, cellular growth and contribute to tumorogenicity by negatively regulating apoptosis and transmitting proliferative and angiogenic signals. Inhibitors of RAF kinase have been shown to block signaling through the MAP kinase signaling pathway.

[004] The RAF kinase family is known to have three members designated C-RAF, also known as RAF-1, B-RAF and A-RAF. It has been reported that B-RAF kinase is commonly activated by one of several somatic point mutations in human cancer, including 59% of the melanoma cell lines tested. See, Davies, H. et al, Nature 417, 949-954 (2002). This invention relates to the discovery of a class of compounds that efficiently inhibit one or more members of the RAF kinase family.

[005] The RAF kinase inhibiting property of the compounds makes them useful as therapeutic agents for the treatment for proliferative diseases characterized by an aberrant MAP kinase signaling pathway, particularly many cancers characterized by overexpression of RAF kinase or an activating mutation of RAF kinase, such as melanoma having mutated B-RAF, especially wherein the mutated B-RAF is the V599E mutant. The present invention also provides a method of treating other conditions characterized by an aberrant MAP kinase signaling pathway, particularly where B-RAF is mutated, for example benign Nevi moles having mutated B-RAF, with the compounds.

Description

[006] A first aspect of the present invention provides a compound of formula (I)



or a pharmaceutically acceptable salt, ester or prodrug thereof for use as a pharmaceutical wherein

each of A_1, A_2, A_3, A_4 is independently selected from N or C-R^3 where R^3 represents H or a substituent moiety of C and where at least one of A_1, A_2 and A_4 is N;

X is a linking moiety selected from N-H, substituted amino, O or S;

R^1 is a substituent of the aromatic ring and n is an integer from 0 to 4;

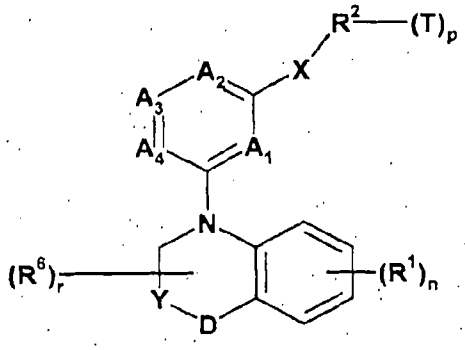
Y and D are independently selected from O, S, CH_2, NH, R^6-substituted C, or R^6-substituted N,

R^6 is a substituent of the ring which contains Y and D and r is an integer from 0 to the maximum number of available valencies of the ring;

R^2 is a substituted or unsubstituted moiety selected from hydrocarbyl and heterocyclic;

T is selected from H, halogen, O-R^9, S-R^8, SO-R^8 SO_2-R^8, SO_2-N(R^8)$_2$, SO_2-$N^a R^{10}$ and SO_2-halogen, where R^8 is selected from hydrogen, substituted or unsubstituted aliphatic, cycloaliphatic, heterocyclyl or aryl; and R^9 is substituted or unsubstituted aliphatic, cycloaliphatic, or aryl, and N^a and R^{10} together represent a 4, 5, 6 ,7 or 8-membered heterocyclic ring including the nitrogen N^a; and p is an integer from 0 to 5.

[007] A second aspect of the invention provides a compound of formula (I)



or a pharmaceutically acceptable salt, ester or prodrug thereof

wherein

each of A_1, A_2, A_3, A_4 is independently selected from N or C-R^3 where R^3 represents H or a substituent moiety of C and where at least one of A_1, A_2 and A_4 is N;

X is a linking moiety selected from N-H, substituted amino, O or S;

R^1 is a substituent of the aromatic ring and n is an integer from 0 to 4;

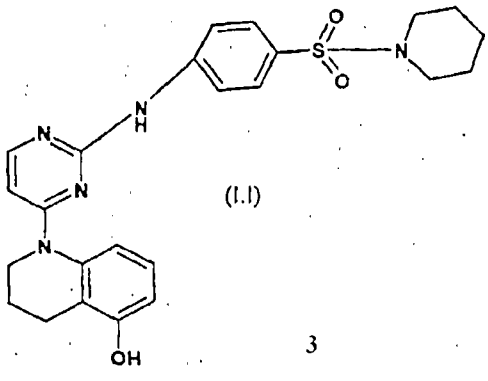
Y and D are independently selected from O, S, CH_2, NH, R^6-substituted C, or R^6-substituted N,

R^6 is a substituent of the ring which contains Y and D and r is an integer from 0 to the maximum number of available valencies of the ring;

R^2 is a substituted or unsubstituted moiety selected from hydrocarbyl and heterocyclic;

T is selected from H, halogen, O-R^8, S-R^8, SO-R^8 SO_2-R^8, SO_2-N(R^8)$_2$, SO_2-NR^{10} and SO_2-halogen, where R^8 is selected from hydrogen, substituted or unsubstituted aliphatic, cycloaliphatic, heterocyclyl or aryl; and R^9 is substituted or unsubstituted aliphatic, cycloaliphatic, or aryl, and NR^{10} represents a heterocyclic ring including the nitrogen; and p is an integer from 0 to 5

and wherein the compound is not:



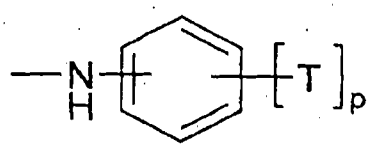
(I.I)

[008] Preferably R^1 is present (n is not 0) and is independently selected from halogen, lower alkyl, halo-lower alkyl, carboxy, esterified carboxy, hydroxy, etherified or esterified hydroxy, lower alkoxy, phenyl, substituted phenyl, lower alkanoyl, substituted or unsubstituted amine, amino, mono- or di- substituted amino, amidino, ureido, mercapto, N-hydroxy-amidino, guanidino, amidino-lower alkyl, sulfo, sulfamoyl, carbamoyl, cyano, cyano-lower alkyl, azo (N=N=N) and nitro.

[009] R^1, or each R^1 independently, is preferably selected from OH, O-alkyl, SH, S-alkyl, halogen, substituted or unsubstituted amine, CF_3 and C_1-C_4 alkyl. Most preferably n is 1.

[0010] R^2 is preferably selected from substituted or unsubstituted aliphatic, alicyclic, or aromatic moieties such as cycloalkyl, heterocyclylalkyl, phenyl, pyrrole, imidazole, pyrazole, isoxazole, oxazole, thiazole, pyridazine, pyrimidine, pyrazine, pyridyl, indole, isoindole, indazole, purine, indolizidine, quinoline, isoquinoline, quinazoline, pteridine, quinolizidine. Preferably R^2 is aromatic. In particular R^2 is selected from substituted or unsubstituted phenyl, imidazolyl, pyrrolyl, oxazolyl and isoxazolyl, and especially R^2 is phenyl or substituted phenyl, wherein the substituent include lower alkyl(C_1-C_6), halogen, OH, lower alkoxy, NH_2, SH, S-alkyl, SO-alkyl, SO_2-alkyl, NH-alkyl, N-dialkyl, carboxyl or CF_3.

[0011] Thus preferably X-R2-$(T)_p$ represents



T may preferably be selected from halogen, O-alkyl, O-alkyl-halogen, SO_2-R^8, SO_2-NHR^8, SO_2-NR^{10} and SO_2-halogen where halogen is preferably chlorine.

[0012] R^8 and R^9 may preferably be independently selected from lower alkyl, especially C_1, C_2, C_3 or C_4 alkyl, cycloalkyl, heterocyclolalkyl, lower alkenyl, lower alkynyl, lower alkoxy, especially methoxy or ethoxy, lower-alkanoyl, carboxy, amino, mono- or di-substituted amino, a cyclic group, for example phenyl, pyrrole, imidazole, pyrazole, isoxazole, oxazole, thiazole, pyridazine, pyrimidine, pyrazine, pyridyl, indole, isoindole, indazole, purine, indolizidine, quinoline, isoquinoline, quinazoline, piperidyl, pteridine, quinolizidine piperazinyl, pyrollidine, morpholinyl and thiomorpholinyl.

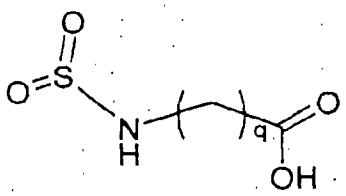
[0013] Preferably R8 and R9 are substituted or unsubstituted alkyl or substituted or unsubstituted aryl. In particular R8 may represent linear or branched alkyl, cycloalkyl, linear or branched halo-alkyl, alkoxy, carboxyalkyl, or alkylamino.

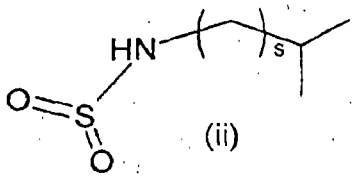
[0014] Most preferably R2 is phenyl and T is located para to the linking group X.

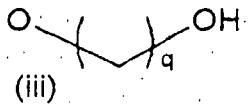
[0015] Where T is O-R9 and R2 is phenyl, preferably T is located meta to the linking group X.

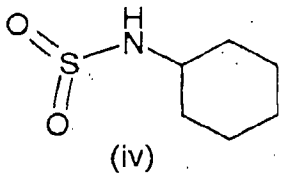
[0016] Preferably p is 1.

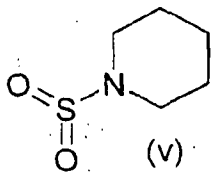
[0017] Particularly preferably T is a moiety selected from the formulae (i) to (x):

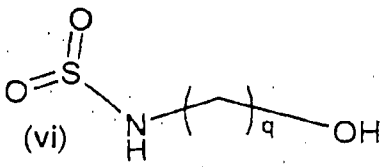

(i)

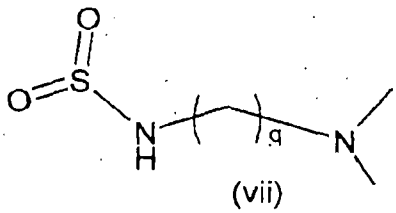

(ii)

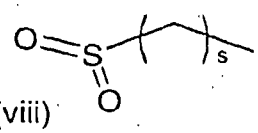

(iii)

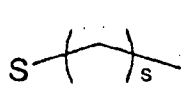

(iv)


(v)


(vi)


(vii)


(viii)


(ix)


(x)

(where q is an integer from 1 to 4 and s is an integer from 0 to 4):

[0018] Preferably A_1 and A_2 are N, and A_3 and A_4 are C-R^3. It is especially preferred that A_3 and A_4 are C-H.

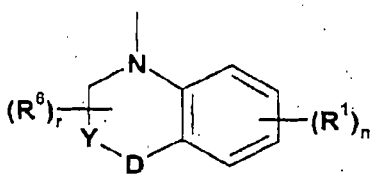
[0019] Preferably X is N-H.

[0020] Preferably R^1 is OH.

[0021] Preferably Y is CH_2. Preferably D is CH_2.

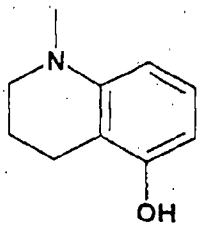
[0022] Preferably each R^3 and R^6 (where present) respectively are independently selected from hydrogen, halogen, lower aliphatic (especially lower alkyl), halo-lower alkyl, carboxy, lower alkoxycarbonyl, hydroxy, etherified or esterified hydroxy, lower alkoxy, optionally substituted alicyclic group or an optionally substituted aromatic group, lower alkanoyloxy, lower alkanoyl, amino, mono- or di- substituted amino, amidino, ureido, mercapto, N-hydroxy-amidino, guanidino, amidino-lower alkyl, sulfo, sulfamoyl, carbamoyl, cyano, cyano-lower alkyl, azo (N=N=N) and nitro. Most preferably r is 0. However, where r is not 0, preferably R^6, or each R^6 independently, is preferably selected from OH, O-alkyl, SH, S-alkyl, halogen, CF_3 and C_1-C_4 alkyl.

[0023] In preferred embodiments of the invention the moiety of formula (I).II



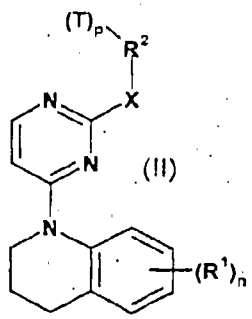
(I.II)

is a tetrahydroquinoline moiety wherein preferably r = 0. Preferably n = 1. Preferably R^1 is OH so that the moiety is a hydroxy tetrahydroquinoline, most especially 1,2,3,4-tetrahydroquinolin-5-ol (formula (I.III):

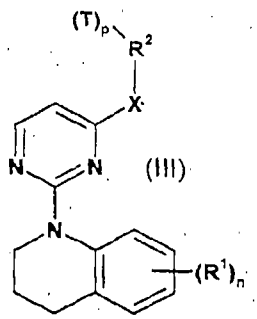


(I.III)

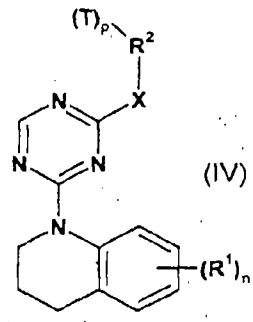
[0024] Preferred compounds include compounds of the formulae (II), (III) and (IV):



(II)



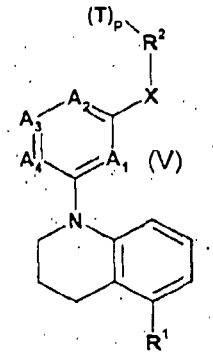
(III)



(IV)

preferably wherein X is NH, R^2 is phenyl n is 1and/or p is 1.

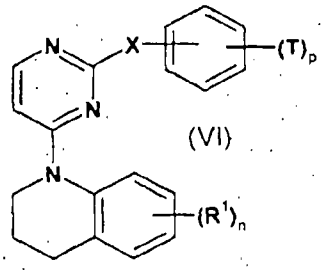
[0025] Other preferred compounds have the formula (V):



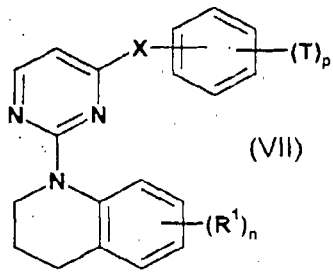
(V)

preferably wherein A_1 and A_2 are N, and A_3 and A_4 are C-R^3.

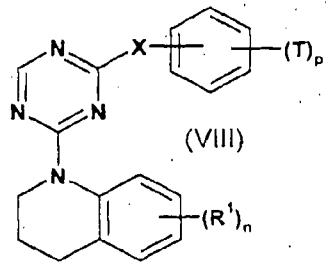
[0026] Further preferred compounds have the formulae (VI), (VII) and (VIII):



(VI)



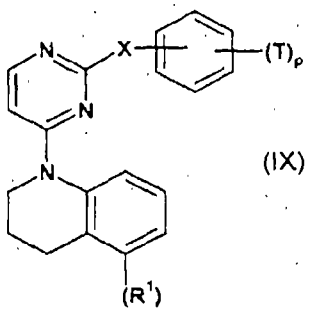
(VII)



(VIII)

preferably wherein n is 1.

[0027] Still further preferred compounds have the formula (IX)

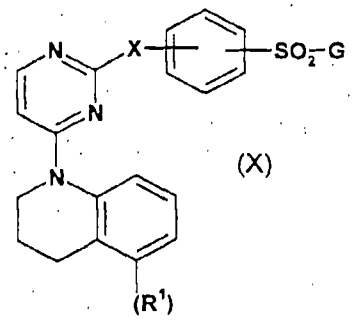


(IX)

[0028] For compounds of formulae (VI) to (IX) preferably p is 1 and X is NH.

[0029] Other preferred compounds include:

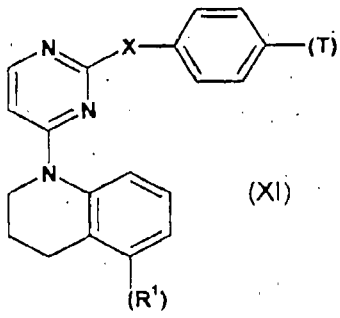
formula (X)



(X)

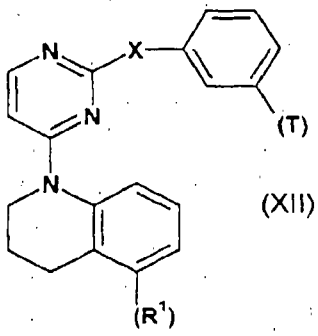
wherein G represents R^8, NHR^8 or NR^{10} and preferably wherein X is NH;

formula (XI);



(XI)

and formula (XII)

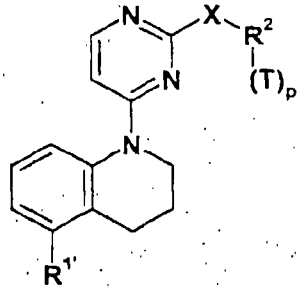


(XII)

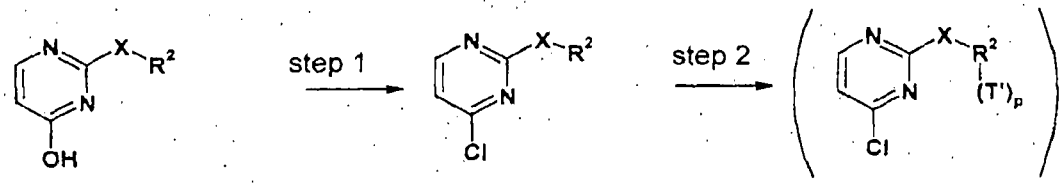
[0030] Preferably in the compound of formula (XII) T is O-R^9.

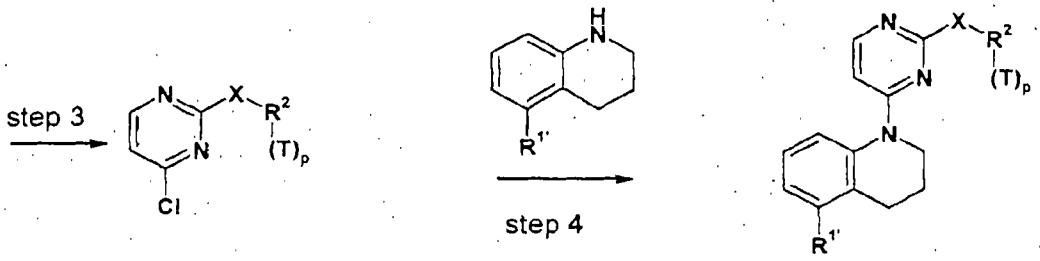
[0031] Preferably in compounds (XI) and (XII) X is NH.

[0032] A third aspect of the invention provides a process for the preparation of a compound of the formula:



which process comprises the following reaction scheme:





where step 2 is optional and where carried out T' is a precursor of T, and $R^{1'}$ is a precursor of R^1 or is R^1 and X, R^1, R^2, T and P are as defined in claim 1.

[0033] Preferably X is NH.

[0034] Preferably R^2 is phenyl.

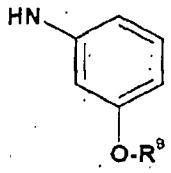
[0035] Preferably p is 1.

[0036] Preferably $R^{1'}$ is OH.

[0037] In one preferred embodiment T represents SO_2-G where G represents R^8, NHR^8 or NR^{10} and R^8 and R^{10} are as defined in the first aspect of the invention.

[0038] In another preferred embodiment T represents O-R^9 where R^9 is as defined in the first aspect of the invention.

[0039] Preferably in the latter embodiment X-R^2-$(T)_p$ represents



[0040] Another aspect of the present invention is a compound of formula (I),

wherein

A_1, A_2, A_3 and A_4 are N or CR_3, and where at least one of A_1, A_2 and A_4 is N;

X is N-R_5, O or S;

R^1 is OH, -O-alkyl, -SH, -S-alkyl, halogen, substituted or unsubstituted amines, $-CF_3$ or $-C_1$-C_4-alkyl;

Y is O, S, CR_5 or NR^5;

D is O, S, CR_5 or NR^5;

R^2 is an alkyl, alicycle, heterocycle, aliaromatic, hetereoaromatic all of which may be substituted or unsubstituted;

T is H, $-SO_2$-NH-R^4 or $-SO_2$-R^4;

R^4 is H, alkyl or aryl, which may be substituted or unsubstituted;

R^5 is H or alky or C(O)-O-C-Ph;

n is 0-4;

or a tautomer thereof, or a salt thereof.

[0041] Special preference is given to a compound of formula (I),

wherein

A_1 and A_2 are N;

A_3 and A_4 are CH;

Y is CH_2 or NR^5 such as -NH-C(O)-O-C-Ph;

X is NH;

D is CH_2;

R^1 is OH, Cl, Me or F;

R^2 is phenyl, imidazolyl, pyrrolyl, oxazolyl or isoxzole, where phenyl may be unsubstituted or substituted with 1, 2 or 3 -OMe groups, Cl, CF_3, -SMe, OH, -O-$[CH_2]_2$-pyridine, -O-$[CH_2]_3$-Cl or -O-$[CH_2]_3$-morpholino; and

R^4 is H, C_2NMe, C_2OH, -Npipeidinyl, Me, Me(t-butyl), C_2COOH or ethyl(isopropyl);

R^5 is H;

n is 0 or 1;

or a tautomer thereof, or a salt thereof.

[0042] More generally, within the context of the present disclosure, the general terms used herein to describe compounds of formulae (I to XII) have the following meanings, unless indicated otherwise.

[0043] Hydrocarbyl may be defined as having preferably up to 20 carbon atoms, especially up to 12 carbon atoms. Hydrocarbyl groups may be linear or branched aliphatic, e.g. alkyl, alkenyl or alkynyl; they may be alicyclic (i.e. aliphatic-cyclic), e.g. cycloalkyl; they may be aromatic, e.g. phenyl. Hydrocarbyl groups may contain a combination of two or more moieties selected from aliphatic, alicyclic and aromatic moieties, e.g. a combination of at least one alkyl group and an aromatic group. In some instances, hydrocarbyl groups may be optionally interrupted by one or more in-chain heteroatoms, for example -O-, thus forming, for example, an ether linkage.

[0044] A mono- or di- substituted amino moiety may be defined where the amino is optionally substituted by a hydrocarbyl moiety, the hydrocarbyl moiety being, for example, selected from lower alkyl, especially C_1, C_2, C_3 or C_4 alkyl, cycloalkyl, especially cyclohexyl, alkyl-carboxy, carboxy, lower alkanoyl, especially acetyl, a carbocyclic group, for example cyclohexyl or phenyl, a heterocyclic group; where the hydrocarbyl moiety is unsubstituted or substituted by, for example lower alkyl (C_1, C_2, C_3, C_4, C_5 , C_6 or C_7), halogen, OH, lower alkoxy, NH_2, SH, S-alkyl, SO-alkyl, SO_2-alkyl, NH-alkyl, N-dialkyl, carboxyl, CF_3, wherein alkyl may be optionally substituted branched, unbranched or cyclic C_{1-6}, interrupted 0-3 times by O, S, N.

[0045] As used herein, the term mercapto defines moieties of the general structure -S-R_e wherein R_e is selected from H, alkyl, a carbocylic group and a heterocyclic group as described herein.

[0046] As used herein, the term guanidino defines moieties of the general structure -NHR-C(NH)NH_2 and derivatives thereof, in particular, where hydrogen is replaced by alkyl, e.g. methyl or ethyl.

[0047] As used herein, the term amidino defines moieties of the general structure -C(NH)NH_2 and derivatives thereof, in particular, where hydrogen is replaced by alkyl, e.g. methyl or ethyl.

[0048] Alkyl preferably has up to 20, more preferably up to 12 carbon atoms and is linear or branched one or more times; preferred is lower alkyl, especially preferred is C_1-C_4-alkyl, in particular methyl, ethyl or i-propyl or t-butyl. Where alkyl may be substituted by one or more substituents. Unsubstituted alkyl, preferably lower alkyl, is especially preferred.

[0049] Alkyl may be optionally interrupted by one or more in-chain heteroatoms, for example -O-, thus forming, for example, an ether linkage.

[0050] Substituted alkyl is alkyl as last defined, especially lower alkyl, preferably methyl; where one or more, especially up to three, substituents may be present, primarily from the group selected from halogen, especially fluorine, amino, N-lower alkylamino, N,N-di-lower alkylamino, N-lower alkanoylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, and phenyl-lower alkoxycarbonyl. Trifluoromethyl is especially preferred. One class of compounds includes a substituted alkyl where the alkyl is substituted with a heterocyclic ring, for example a pyrazine ring, thus forming an alkylene-het group, i.e. -CH_2-Het, the alkyl group effectively acting as a linker between the heterocycle and a second moiety.

[0051] The term "lower" when referring to substituents such as alkyl, alkoxy, alkyl amine, alkylthio and the like denotes a radical having up to and including a maximum of 7, especially from 1 up to and including a maximum of 4, carbon atoms, the radicals in question being unbranched or branched one or more times.

[0052] The alkyl portion of lower alkyl, lower alkoxy, mono- or di-lower alkyl amino, lower alkyl thio and other substituents with an alkyl portion is especially C_1-C_4alkyl, for example n-butyl, sec-butyl, tert-butyl, n-propyl, isopropyl, methyl or ethyl. Such alkyl substituents are unsubstituted or substituted by halogen, hydroxy, nitro, cyano, lower alkoxy, C_3, C_4, C_5, C_6 or C_7 cycloalkyl, amino, or mono- or di-lower alkyl amino, unless otherwise indicated.

[0053] Halo-lower alkyl, halo-lower alkyloxy, halo-lower alkylthio and the like refer to substituents having an alkyl portion wherein the alkyl portion is mono- to completely substituted by halogen. Halo-lower alkyl, halo-lower alkyloxy, halo-lower alkylthio and the like are included within substituted lower alkyl, substituted lower alkoxy, substituted lower alkylthio and the like.

[0054] Among the moieties corresponding to substituted alkyl, hydroxy-lower alkyl, especially 2-hydroxyethyl, and/or halo-lower alkyl, especially trifluoromethyl or 2,2,2-trifluoroethyl, are especially preferred.

[0055] An alicyclic group is a carbocyclic group especially which comprises 3, 4, 5, 6 or 7 in ring carbon atoms and is non aromatic, but may be saturated or unsaturated. Preferred alicyclic groups comprise cycloalkyl groups, which are preferably C_3-C_{10}-cycloalkyl, especially cyclopropyl, dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, cycloalkyl being unsubstituted or substituted by one or more, especially 1, 2 or 3, substituents.

[0056] An aromatic group is heterocyclic or carbocyclic and is bound via a bond located at an aromatic ring carbon atom of the radical (or optionally bound via a linking

group, such as -O- or -CH_2-). Preferably the aromatic group is carbocyclic and has a ring system of not more than 16 carbon atoms and is preferably mono- bi- or tri- cyclic and may be fully or partially substituted, for example substituted by at least two substituents. Preferably, the aromatic group is selected from phenyl, naphthyl, indenyl, azulenyl and anthryl, and is preferably in each case unsubstituted or substituted by lower alkyl, especially methyl, ethyl or n-propyl, halo (especially fluoro, chloro, bromo or iodo), halo-lower alkyl (especially trifluoromethyl), hydroxy, lower alkoxy (especially methoxy), halo-lower alkoxy (especially 2,2,2-trifluoroethoxy), amino-lower alkoxy (especially 2-amino-ethoxy), lower alkyl (especially methyl or ethyl) carbamoyl, N-(hydroxy-lower alkyl)-carbamoyl (especially N-(2-hydroxyethyl)-carbamoyl) and/or sulfamoyl-substituted aryl, especially a corresponding substituted or unsubstituted phenyl.

[0057] A substituted aromatic group is generally an aromatic group that is substituted with from 1-5, preferably 1 or 2, substituents. Appropriate substituents include, but are not limited to, amino, mono- or di-lower alkyl substituted amino, wherein the lower alkyl substituents may be unsubstituted or further substituted by those substitutents listed above for alkyl groups, halogen, lower alkyl, substituted lower alkyl, hydroxy, lower alkoxy, substituted lower alkoxy, nitro, cyano, mercapto, lower alkylthio, halo-lower alkylthio, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, lower alkanoyl, carbamoyl, and N-mono- or N,N-di-lower alkyl substituted carbamoyl, wherein the lower alkyl substitents may be unsubstituted or further substituted.

[0058] A heterocycle is an aromatic ring or ring system having 16 or fewer members, preferably a ring of 5 to 7 members. Heterocycle also includes a three to ten membered non-aromatic ring or ring system and preferably a five- or six-membered non-aromatic ring, which may be fully or partially saturated. In each case the rings may have 1, 2 or 3 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur. The heterocycle is unsubstituted or substituted by one or more, especially from one to three, for example one, identical or different substituents. Important substituents on heterocycle are those selected from the group consisting of halogen, for example, fluorine or chlorine; mono- or di-lower alkyl-substituted amino wherein the alkyl groups are unsubstituted or substituted by halogen, hydroxy, nitro, cyano, lower alkoxy, C_3-C_7 cycloalkyl, a heterocyclic radical or a heteroaryl radical; lower alkyl, such as methyl or ethyl; halo-lower alkyl, such as trifluoromethyl; lower alkoxy, such as methoxy or ethoxy; halo-lower alkoxy, for example, trifluoromethoxy; lower alkylthio, such as methylmercapto, halo-lower alkylthio, such as trifluoromethylthio, a heteroaryl radical, heteroaryl-lower-alkylene, a heterocyclic radical or heterocyclic-lower-alkylene.

[0059] Heterocycle especially is a radical selected from the group consisting of oxiranyl, azirinyl, 1,2-oxathiolanyl, imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2*H*-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, pyranyol, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, especially piperidin-1-yl, piperazinyl, especially piperazin-1-yl, pyridazinyl, morpholinyl, especially morpholino, thiomorpholinyl, especially thiomorpholino, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl and chromanyl, each of these radicals being unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl, especially methyl or tert-butyl, lower alkoxy, especially methoxy, and halo, especially bromo or chloro. Unsubstituted heterocyclyl, especially piperidyl, piperazinyl, thiomorpholino or morpholino, is preferred.

[0060] Halogen is especially fluorine, chlorine, bromine or iodine, more especially fluorine, chlorine or bromine, in particular fluorine.

[0061] Cycloalkyl is preferably C_3-C_{10}-cycloalkyl, especially cyclopropyl, dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, cycloalkyl being unsubstituted or substituted by one or more, especially 1 to 3, substituents.

[0062] Heterocyclylalkyl is as cycloalkyl but containing one or more in-ring heteroatoms and may be exemplified by piperidyl, piperazinyl, pyrollidine, morpholinyl.

[0063] Esterified carboxy is especially lower alkoxycarbonyl, such as tert-butoxycarbonyl, iso-propoxycarbonyl, methoxycarbonyl or ethoxycarbonyl, phenyl-lower alkoxycarbonyl, or phenyloxycarbonyl.

[0064] Alkanoyl is primarily alkylcarbonyl, especially lower alkanoyl, e.g. acetyl. In particular, the alkanoyl group may be substituted by substituents, e.g. CO-R

[0065] Any reference to compounds, salts and the like in the plural is always to be understood as including one compound, one salt or the like.

[0066] Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and

"comprises", means "including but not limited to", and is not intended to (and does not) exclude other moieties, additives, components, integers or steps.

[0067] Any asymmetric carbon atoms may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. Radicals having any unsaturation are present in cis-, trans- or (cis, trans) form. The compounds may thus be present as mixtures of isomers or as pure isomers, preferably as enantiomer-pure diastereomers.

[0068] The invention relates also to possible tautomers of the disclosed compounds.

[0069] 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 for example may be separated into their individual diastereomers by means of fractionated crystallization, 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 or formulae II to XII respectively. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

[0070] Salts are especially the pharmaceutically acceptable acid addition salts of compounds of formula (I). Such salts are formed, for example, by compounds of formula (I) having a basic nitrogen atom as acid addition salts, preferably with organic or inorganic acids, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, hydrohalic acids, such as hydrochloric acid; sulfuric acid; or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2-hydroxybutyric acid, gluconic acid, glucosemonocarboxylic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids, such as glutamic acid, aspartic acid, N-methylglycine, acetylaminoacetic acid, N-acetylasparagine, N-acetylcysteine, pyruvic acid, acetoacetic acid, phosphoserine, 2- or 3-glycerophosphoric acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, benzoic acid, salicylic acid, 1- or 3-hydroxynaphthyl-2-carboxylic acid, 3,4,5-trimethoxybenzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, glucuronic acid, galacturonic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalenedisulfonic acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

[0071] For isolation or purification it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. Only the pharmaceutically acceptable salts or the free compounds (optionally in the form of pharmaceutical compositions) are used therapeutically, and those are therefore preferred.

[0072] In view of the close relationship between the novel compounds in free form and in the form of their salts, including also those salts which can be used as intermediates, for example in the purification of the novel compounds or for their identification, hereinbefore and hereinafter any reference to the free compounds is also to be understood as including the corresponding salts, as appropriate and expedient.

[0073] The compounds of the present invention are found to inhibit, regulate and/or modulate tyrosine and serine/threonine kinase and kinase-like proteins involved in signal transduction, and compositions containing the compounds are used in the treatment of tyrosine and serine/threonine kinase and kinase-like-dependent diseases, such as angiogenesis, cancer, tumour growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, neurotraumatic diseases, chronic neurodegeneration, pain, migraine or cardiac hypertrophy, and the like in mammals.

[0074] Specifically, the compounds of the present invention inhibit IKK, PDGF-R, Kdr, c-Src, Her-1, Her-2, c-Kit, c-Abl, Ins-r, Tek, Flt-1, Flt-3, Flt-4, c-Abi and FGFR-1, Eph receptors (e.g. EphB4), CDK1, CDK2 and RET at >70% inhibition at 10 micromole. More specifically, the compounds inhibit the RAF family of kinases including mutations with IC50 values in the range of 1-1000 nM.

[0075] Typically, the patient is a mammal, generally a human, suffering from a disease that is characterized by excessive signaling through the MAP kinase pathway. This can be measured by activation state specific antibodies to pathway members by methods such as Western blot analysis or immunohistochemistry. Such methods are known to those of skill in the art.

[0076] In general, the disease characterized by excessive signaling through the MAP kinase signaling pathway is a proliferative disease, particularly a cancer characterized by increased RAF kinase activity, for example one which overexpresses wild-type B- or C-RAF kinase, or that expresses an activating mutant RAF kinase, for example a mutant B-RAF kinase. Cancers wherein a mutated RAF kinase has been detected include melanoma, colorectal cancer, ovarian cancer, gliomas, adenocarcinomas, sarcomas, breast cancer and liver cancer. Mutated B-RAF kinase is especially prevalent in many melanomas.

[0077] In accordance with the present invention, a sample of diseased tissue may taken from the patient, for example, as a result of a biopsy or resection, and tested to determine whether the tissue produces a mutant RAF kinase, such as a mutant B-RAF kinase or overexpresses a wild-type RAF kinase, such as wild-type B- or C-RAF kinase. If the test indicates that mutant RAF kinase is produced or that a RAF kinase is overproduced in the diseased tissue, the patient is treated by administration of an effective RAF-inhibiting amount of a RAF inhibitor compound described herein.

[0078] However, it is also possible to downregulate the MAP kinase signaling pathway with a RAF kinase inhibiting compound if another kinase in the cascade is the cause of excessive signaling in the pathway. Thus, the present invention further relates to the treatment of a disease characterized by excessive signaling in the MAP kinase signaling pathway attributed to a cause other than an activating mutation in or overexpression of a RAF kinase.

[0079] Tissue samples are tested by methods generally known in the art. For example, B-RAF mutations are detected by allele specific PCR, DHPLC, mass spectropscopy and overexpression of wild-type B- or C-RAF detected by immunohistochemistry, immunofluorescense, or Western blot analysis. A particularly useful method of detecting B-RAF mutations is a polymerase chain reaction based method. Similar methods are used to determine whether other kinases in the cascade are mutant or overexpressed.

[0080] A particularly important aspect of this invention relates to a method of treating melanoma, which comprises (a) testing melanoma tissue from a patient to determine whether the melanoma tissue expresses mutant RAF kinase or overexpresses a wild-type RAF kinase and (b) treating the patient with an effective RAF kinase inhibiting amount of a RAF-inhibiting compound described herein if the melanoma tissue is found to overexpress a wild type RAF kinase or express an activating mutant B-RAF kinase.

[0081] An important aspect of this embodiment relates to a method of treating melanoma, which comprises (a) testing melanoma tissue from a patient to determine whether the melanoma tissue overexpresses B-RAF kinase or C-RAF kinase activity and (b) treating the patient with an effective RAF kinase inhibiting amount of a RAF inhibiting compound described herein if the melanoma tissue is found to overexpress the B-RAF kinase or C-RAF kinase activity.

[0082] Another important aspect of this embodiment relates to a method of treating melanoma, which comprises (a) testing melanoma tissue from a patient to determine whether the melanoma tissue expresses mutant B-RAF kinase and (b) treating the patient with an effective RAF kinase inhibiting amount of a RAF inhibiting compound described herein if the melanoma tissue is found to express mutant B-RAF kinase.

[0083] Generally, the B-RAF kinase mutation is one of those described in the Davies et al article cited. These mutations are summarized in Table 1.

[0084] Thus, the present invention particularly relates to a method of treating a disease characterized by an activated mutant B-RAF kinase, which comprises detecting a mutation in the B-RAF kinase gene or protein in a tissue sample from a patient and treating the patient with an effective B-RAF kinase inhibiting compound, especially a compound described herein.

[0085] Hence, the present invention additionally relates to a compound (for example of formulae I to XII) for use in the treatment of melanoma. More particularly, the invention relates to a compound for use in the treatment of a disease characterized by an activated mutant B-RAF kinase.

Table 1

B-RAF mutation	protein change
G1388A	G463E
G1388T	G463V
G1394C	G465A
G1394A	G465E
G1394T	G465V
G1403C	G468A
G1403A	G468E
G1753A	E585K
T1782G	F594L
G1783C	G595R
C1786G	L596V
T1787G	L596R
T1796A	V599E
TG1796-97AT	V599D

[0086] Further, the invention provides for the use of a compound (for example of formulae I to XII) in the manufacture of a medicament for use in the treatment of melanoma. More specifically, the invention provides for the use of a compound in the manufacture of a medicament for use in the treatment of a disease characterized by an activated mutant B-RAF kinase.

[0087] An important aspect of this invention includes those instances wherein the mutant B-RAF kinase exhibits a mutation described in Table 1, especially the V599E mutation.

[0088] A particularly important aspect of this invention includes those instances wherein disease is melanoma and the mutant B-RAF kinase exhibits a mutation described in Table 1, especially the V599E mutation.

[0089] Accordingly, this invention includes a method of treating a disease characterized by mutant B-RAF kinase, which comprises detecting a mutation in the B-RAF kinase gene selected from G1388A, G1388T, G1394C, G1394A, G1394T, G1403C, G1403A, G1753A, T1782G, G1783C, C1786G, T1787G, T1796A and TG1796-97AT, or corresponding mutation in the RAF kinase protein, in a tissue sample from a patient and treating the patient with an effective B-RAF kinase inhibiting compound described herein.

[0090] The present invention further relates to a method of inhibiting RAF kinase, which comprises contacting the RAF kinase with a compound of formula (I), or more specifically with any one of the compounds of formulae (II) to (XII). Preferably, the RAF kinase is B- or C-RAF kinase, or a mutant RAF kinase, especially a mutant B-RAF kinase, particularly the V599E mutant. The RAF kinase may be isolated or in a cellular environment.

[0091] The compounds of formula (I), and more specifically the compounds of formulae (II) to (XII) have valuable pharmacological properties, as described above.

[0092] The compounds of the present invention may be administered alone or in combination with other anticancer agents, such as compounds that inhibit tumor angiogenesis, for example, the protease inhibitors, epidermal growth factor receptor kinase inhibitors, vascular endothelial growth factor receptor kinase inhibitors and the like; cytotoxic drugs, such as antimetabolites, like purine and pyrimidine analog antimetabolites; antimitotic agents like microtubule stabilizing drugs and antimitotic alkaloids; platinum coordination complexes; anti-tumor antibiotics; alkylating agents, such as nitrogen mustards and nitrosoureas; endocrine agents, such as adrenocorticosteroids, androgens, anti-androgens, estrogens, anti-estrogens, aromatase inhibitors, gonadotropin-releasing hormone agonists and somatostatin analogues and compounds that target an enzyme or receptor that is overexpressed and/or otherwise involved a specific metabolic pathway that is upregulated in the tumor cell, for example ATP and GTP phosphodiesterase inhibitors, protein kinase inhibitors, such as serine, threonine and tyrosine kinase inhibitors, for example, Abelson protein tryosine kinase and the various growth factors, their receptors and kinase inhibitors therefore, such as, epidermal growth factor receptor kinase inhibitors, vascular endothelial growth factor receptor kinase inhibitors, fibroblast growth factor inhibitors, insulin-like growth factor receptor inhibitors and platelet-derived growth factor receptor kinase inhibitors and the like; methionine aminopeptidase inhibitors, proteasome inhibitors, cyclooxygenase inhibitors, for example, cyclooxygenase-1 or –2 inhibitors, and histone deacetylase inhibitors.

[0093] The compound of the present invention may also be administered together with radiotherapy, immunotherapy, surgical treatment or combinations thereof. Treatment to

maintain the status of a patient after tumor remission or even chemopreventive treatment, for example in the case of at-risk patients, is also possible.

[0094] Compounds according to the invention are intended not only for the (prophylactic and, preferably, therapeutic) treatment of human beings, but also for the treatment of other warm-blooded animals, for example of commercially useful animals, for example rodents, such as mice, rabbits or rats, or guinea pigs.

[0095] In general, the invention relates also to the use of a compound of formula (I), and more specifically to the use of compounds of formulae (II) to (XII), in inhibiting RAF kinase activity.

[0096] The compounds of the present invention are preferably administered as an active ingredient in a pharmaceutical composition. Preference is given to a pharmaceutical composition which is suitable for administration to a warm-blooded animal, especially a human being or a commercially useful mammal, which is suffering from a disease characterized by an aberrant MAP kinase signaling pathway especially, a tumor disease, most particularly melanoma, comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof where salt-forming groups are present, in an amount that is effective in inhibiting RAF kinase, particularly a mutant RAF kinase, together with at least one pharmaceutically acceptable carrier.

[0097] Preference is given also to a pharmaceutical composition for the prophylactic or, especially, therapeutic treatment of tumor diseases and other proliferative diseases in a warm-blooded animal, especially a human being or a commercially useful mammal, which requires such treatment, especially which is suffering from such a disease, comprising a novel compound of formula (I), or a pharmaceutically acceptable salt thereof, as active ingredient in an amount that is effective prophylactically or, especially, therapeutically against the mentioned diseases.

[0098] Pharmaceutical compositions comprise from approximately 1 % to approximately 95 % active ingredient, dosage forms that are in single dose form preferably comprising from approximately 20 % to approximately 90 % active ingredient, and dosage forms that are not in single dose form preferably comprising from approximately 5 % to approximately 20 % active ingredient. Unit dose forms are, for example, dragées, tablets, ampoules, vials, suppositories or capsules. Other dosage forms are, for example, ointments, creams, pastes, foams, tinctures, lipsticks, drops, sprays, dispersions, etc. Examples are capsules comprising from approximately 0.05 g to approximately 1.0 g of the active ingredient.

[0099] The pharmaceutical compositions of the present invention are prepared in a manner employing steps which may individually be known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes.

[00100] Solutions of the active ingredient are preferably used, in addition also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions, which, in the case of, for example, lyophilised compositions which contain the active substance alone or together with a carrier, for example mannitol, can be prepared prior to use. The pharmaceutical compositions may be sterilised and/or comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known per se, for example by means of conventional dissolving or lyophilising processes. The mentioned solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin, or solubilisers, for example Tween 80 [polyoxyethylene(20)sorbitan monooleate; trade mark of ICI Americas, Inc, USA].

[00101] Suspensions in oil comprise as the oily component the vegetable, synthetic or semi-synthetic oils customary for injection purposes. There may be mentioned as such especially liquid fatty acid esters, which comprise as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, optionally with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has a maximum of 6 carbon atoms and is a mono- or poly-hydric, for example mono-, di- or tri-hydric, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or their isomers, but especially glycol and glycerol. Examples of fatty acid esters which may be mentioned are, therefore: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethyleneglycerol trioleate from Gattefossé, Paris), "Labrafil M 1944 CS" (unsaturated polyglycolised glycerides prepared by alcoholysis of apricot kernel oil and composed of glycerides and polyethylene glycol ester; Gattefossé, France), "Labrasol" (saturated polyglycolised glycerides prepared by alcoholysis of TCM and composed of glycerides and polyethylene glycol ester; Gattefossé, France) and/or "Miglyol 812" (triglyceride of saturated fatty acids having a chain length of from C_8 to C_{12} from Hüls AG, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and, more especially, groundnut oil.

[00102] The preparation of the injection compositions is carried out in customary manner under sterile conditions, as are also the introduction thereof, for example, into ampoules or vials and the sealing of the containers.

[00103] Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, granulating a resulting mixture, where appropriate, and processing the mixture or granules, if desired, where appropriate by addition of additional excipients, to tablets or dragée cores.

[00104] Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

[00105] Dragée cores can be provided with suitable, optionally enteric, coatings, there being used inter alia concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

[00106] Pharmaceutical compositions for oral administration are also hard gelatin capsules and soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene glycol or propylene glycol, it likewise being possible to add stabilisers and detergents, for example of the polyoxyethylenesorbitan fatty acid ester type.

[00107] Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base.

Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

[00108] For parenteral administration there are suitable, especially, aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or aqueous injection suspensions that comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran and, if desired, stabilisers. The active ingredient, optionally together with excipients, can also be in the form of a lyophilisate and can be made into a solution prior to parenteral administration by the addition of suitable solvents.

[00109] Solutions used, for example, for parenteral administration can also be used as infusion solutions.

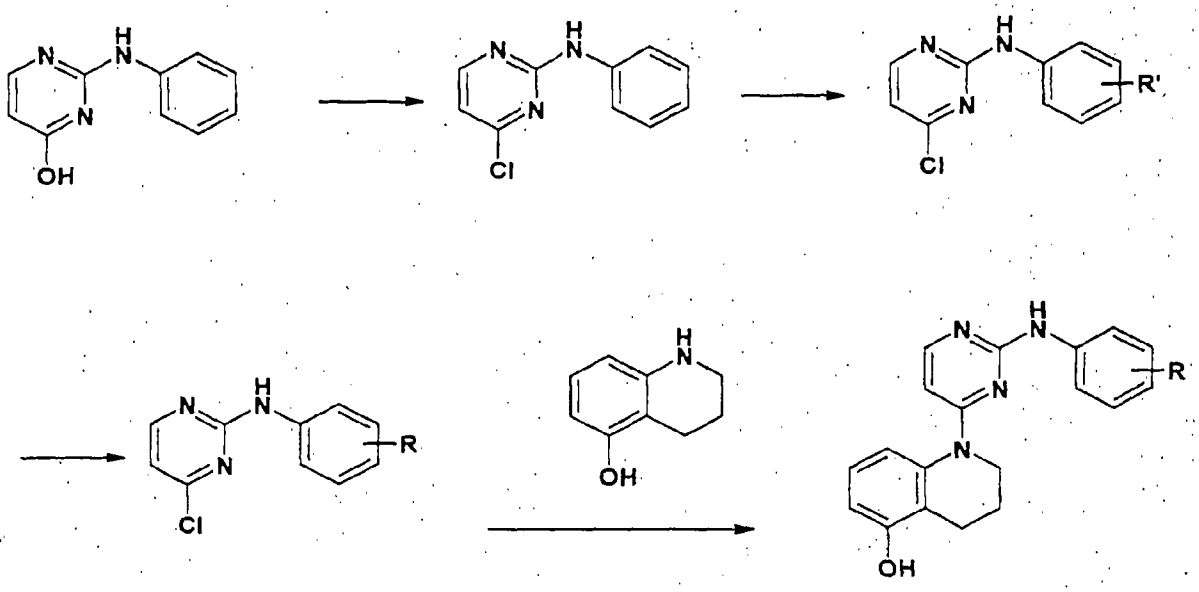
[00110] Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or microbicides, such sorbic acid or benzoic acid.

[00111] The invention relates especially to a process or a method for treating one of the pathological conditions that is characterized by an aberrant MAP kinase signaling pathway, especially a disease responsive to inhibition of RAF kinase, especially a corresponding tumor disease. The compounds of formula (I) can be administered prophylactically or therapeutically as such or in the form of pharmaceutical compositions, preferably in an amount that is effective against the mentioned diseases, to a warm-blooded animal, for example a human being, requiring such treatment, the compounds being used especially in the form of pharmaceutical compositions. In the case of a body weight of approximately 70 kg, a daily dose of from approximately 0.1 g to approximately 5 g, preferably from approximately 0.5 g to approximately 2 g, of a compound of the present invention is administered.

[00112] The preferred dosage, composition and preparation of pharmaceutical formulations (medicaments) to be used in each particular case are described above.

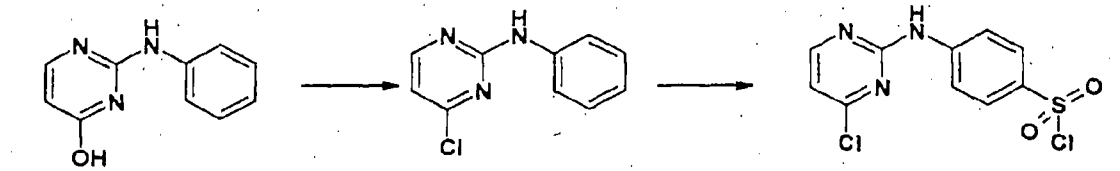
[00113] The compounds of the present invention are prepared utilizing methods preferably according to the exemplary reaction schemes described below, individual steps of the said methods being known in general terms to those skilled in the art.

[00114] A general scheme showing a process of the present invention is as described above. A more specific variation of the above scheme is given below (Scheme G):

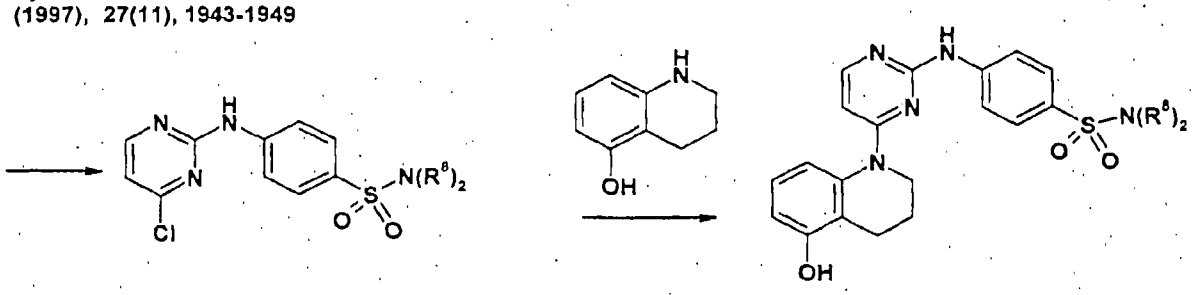


Scheme G

[00115] An example of an R group is one containing sulphur, as illustrated below in Schemes 1 and 2:

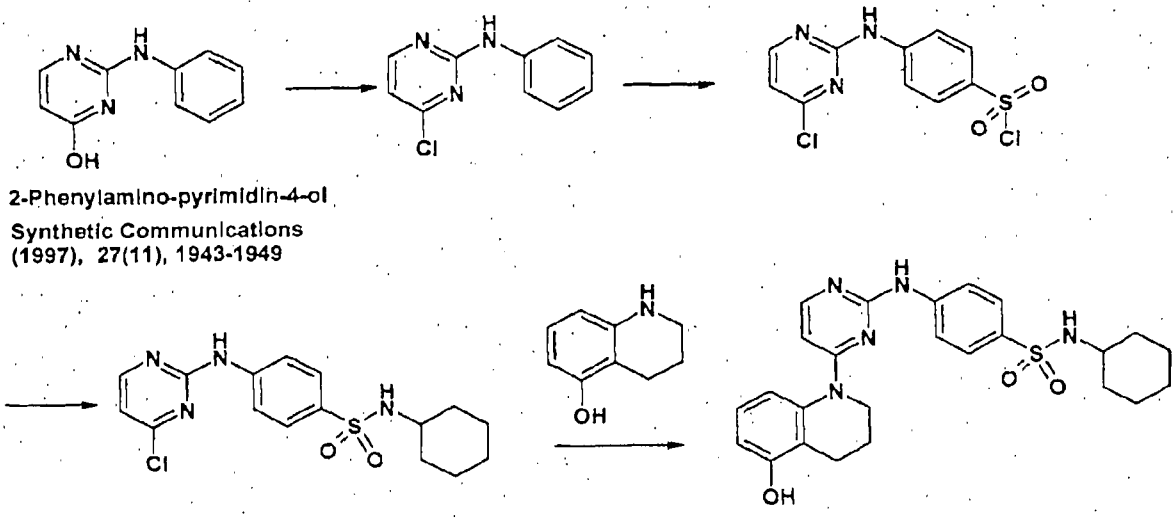


2-Phenylamino-pyrimidin-4-ol
Synthetic Communications
(1997), 27(11), 1943-1949



Scheme 1

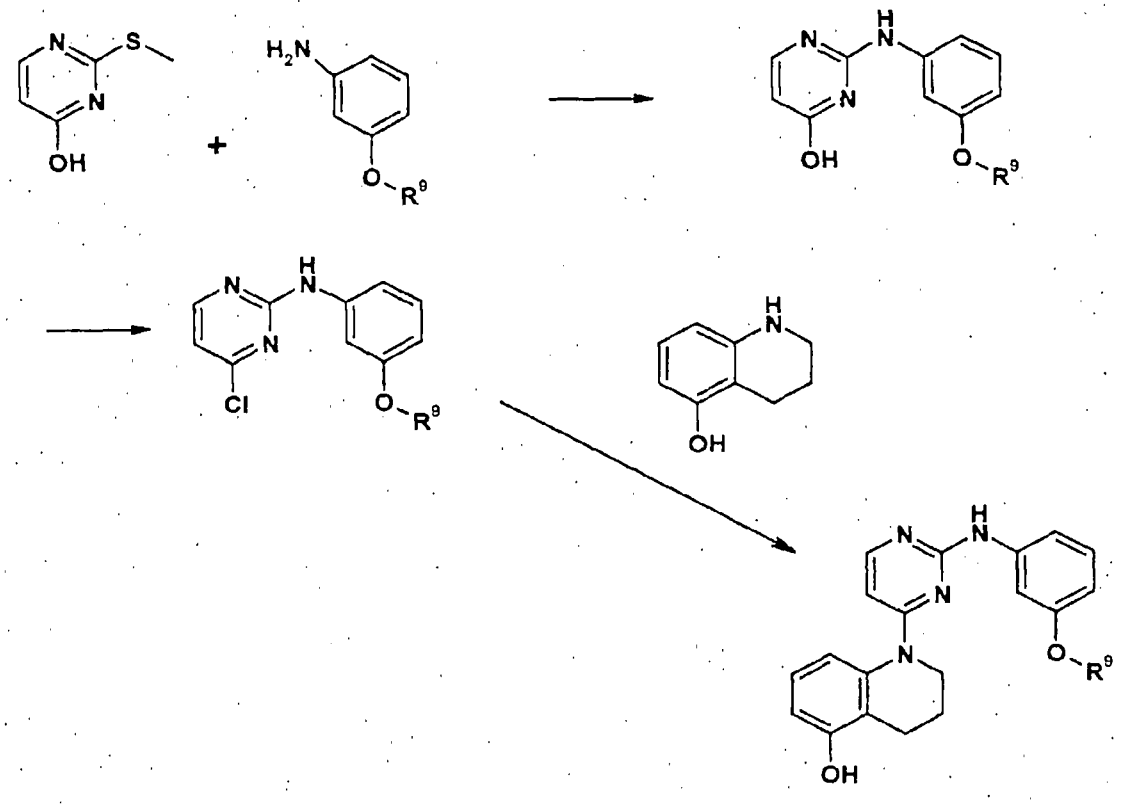
[00116] A particular example of a reaction of Scheme 1 is shown below:



2-Phenylamino-pyrimidin-4-ol
Synthetic Communications
(1997), 27(11), 1943-1949

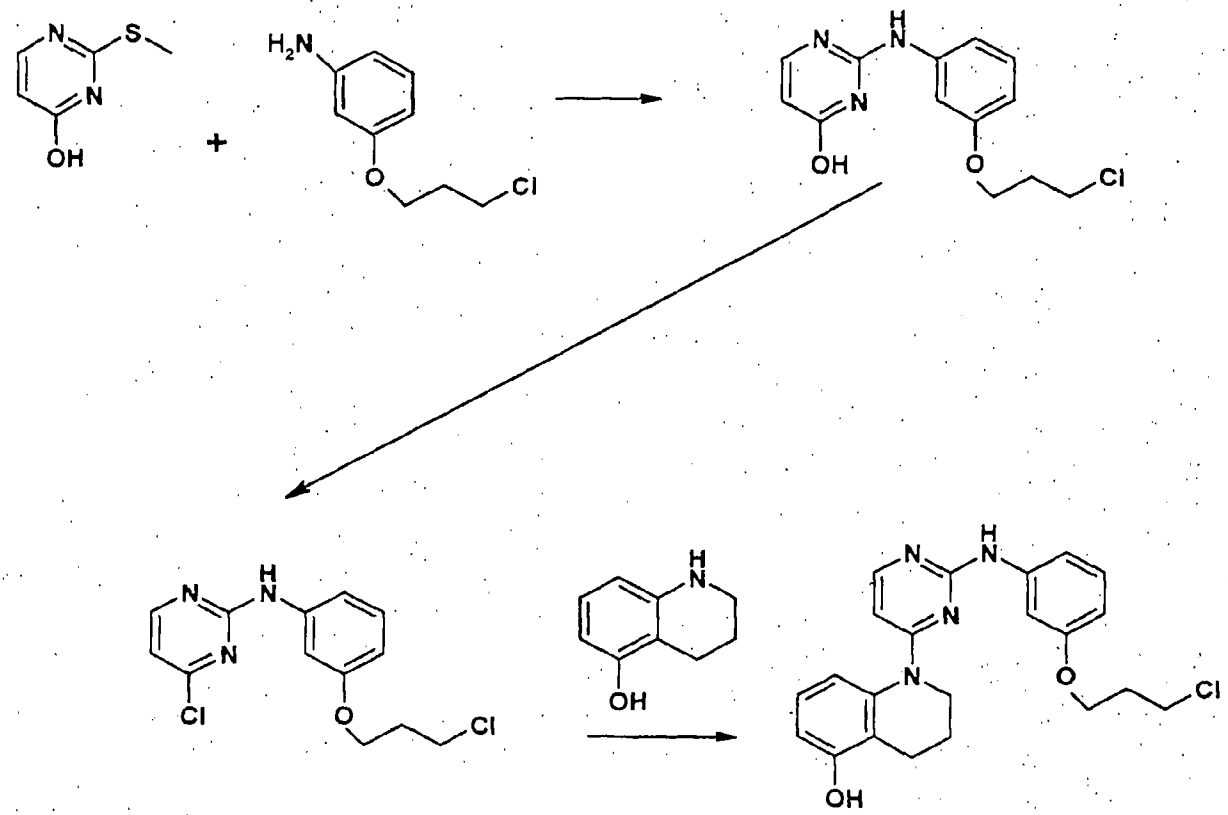
Scheme 2

[00117] A third reaction scheme according to the present invention is shown below:



Scheme 3

[00118] A particular example of reaction Scheme 3 is shown below in Scheme 4.



Scheme 4

Examples

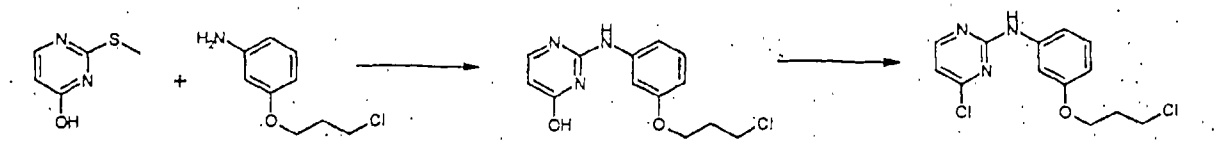
[00119] The preparative method will now be illustrated by reference to the specific preparations of 1-{2-[3-(3-Chloro-propoxy)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-5-ol and various 1-{2-[3-(sulphonyl, sulphanyl and sulphonamino)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-5-ol derivatives.

[00120] Results of melting point tests and mass spectrometric evaluations are also presented.

[00121] 1-{2-[3-(3-Chloro-propoxy)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-5-ol

[00122] Intermediate synthesis:

[00123] [3-(3-Chloro-propoxy)-phenyl]-(4-chloro-pyrimidin-2-yl)-amine:

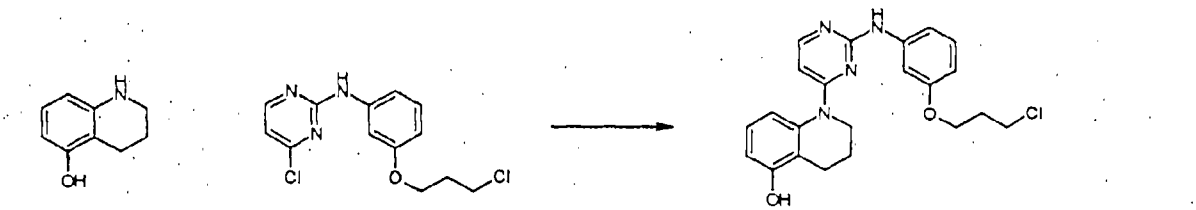


2-Methylsulfanyl-pyrimidin-4-ol | 3-(3-Chloro-propoxy)-phenylamine | 2-[3-(3-Chloro-propoxy)-phenylamino]-pyrimidin-4-ol | [3-(3-Chloro-propoxy)-phenyl]-(4-chloro-pyrimidin-2-yl)-amine

[00124] Heating 22.98 g (161.64 mmol) 2-methylsulfanyl-pyrimidin-4-ol in 90 mL DMEU to 100° C results in a clear solution. Now, 30 g (161.64 mmol) 3-(3-chloro-propoxy)-phenylamine are added. Heating at 100° C is continued for 15 h. A 10 mL fraction of this reaction mixture is poured onto aqueous sodium bicarbonate and extracted with ethyl acetate. After evaporation of the solvent the brown oil is dissolved in 10 mL DMEU and 35 mL $POCl_3$ are added. After heating the reaction mixture at 70° C for 2 h it is carefully poured onto an aqueous bicarbonate solution. Extraction with ethyl acetate followed by flash chromatography on silica (eluent: hexanes ethyl acetate 1:1) affords 1.60 g (yield ca. 50%) of the title compound as brown oil.

^{1}H NMR: (DMSO d_6, 400 MHz): 10.03 (s, 1H), 8.45 (d, 1H), 7.44 (t, 1H), 7.29 (dd, 1H), 7.21 (t, 1H), 6.97 (d, 1H), 6.61 (dd, 1H), 4.07 (t, 2H), 3.80 (t, 2H), 2.18 (quint, 2H).

[00125] 1-{2-[3-(3-Chloro-propoxy)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-5-ol:



3-(3-Chloro-propoxy)-phenylamine | [3-(3-Chloro-propoxy)-phenyl]-(4-chloro-pyrimidin-2-yl)-amine | 1-{2-[3-(3-Chloro-propoxy)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-5-ol

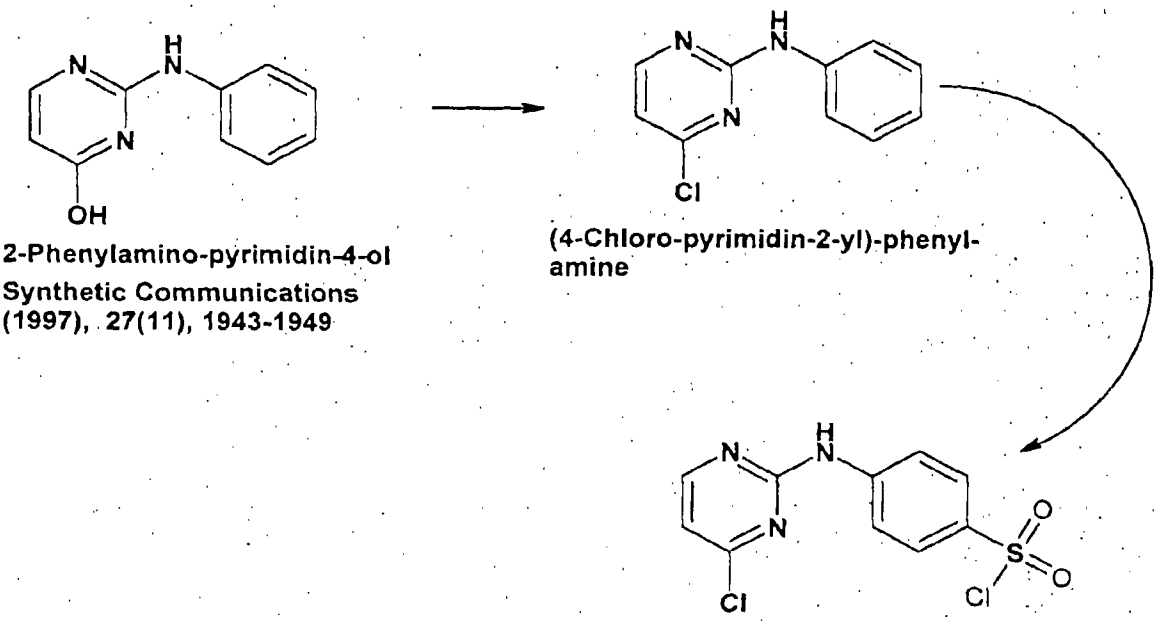
[00126] A mixture of 200 mg (0.617 mmol) [3-(3-chloro-propoxy)-phenyl]-(4-chloro-pyrimidin-2-yl)-amine and 100 mg (0.617 mmol) 3-(3-chloro-propoxy)-phenylamine is heated neat at 100° C for 20 minutes. With the help of sonication the resulting resin is dissolved in a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer is dried over sodium sulfate and evaporated. Chromatography on silica using dichloromethane / ethyl acetate (10:1) as eluent afforded 160 mg (yield 58%) of the title compound as yellow foam.

^{1}H NMR (DMSO d_6, 400 MHz): 9.43 (s, 1H), 9.13 (s, br, 1H), 7.91 (d, 1H), 7.47 (m, 1H), 7.17 (d, 1H), 7.04 (t, 1H), 6.90 (t, 1H), 6.72 (d, 1H), 6.51 (d, 1H), 6.42 - 6.38 (m, 2H), 3.96 (t, 2H), 3.88 (dd, 2H), 3.71 (t, 2H), 2.53 (t, 2H), 2.09 (quint, 2H), 1.78 (m, 2H).

MS: ES+ : 411 $(M+1)^+$ isotop pattern for 1 chlorine atom.

[00127] 1-{2-[3-(sulphonyl, sulphanyl and sulphonamino)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-5-ol derivatives

[00128] Intermediate synthesis:



2-Phenylamino-pyrimidin-4-ol
Synthetic Communications (1997), 27(11), 1943-1949

(4-Chloro-pyrimidin-2-yl)-phenyl-amine

4-(4-Chloro-pyrimidin-2-ylamino)-benzenesulfonyl chloride

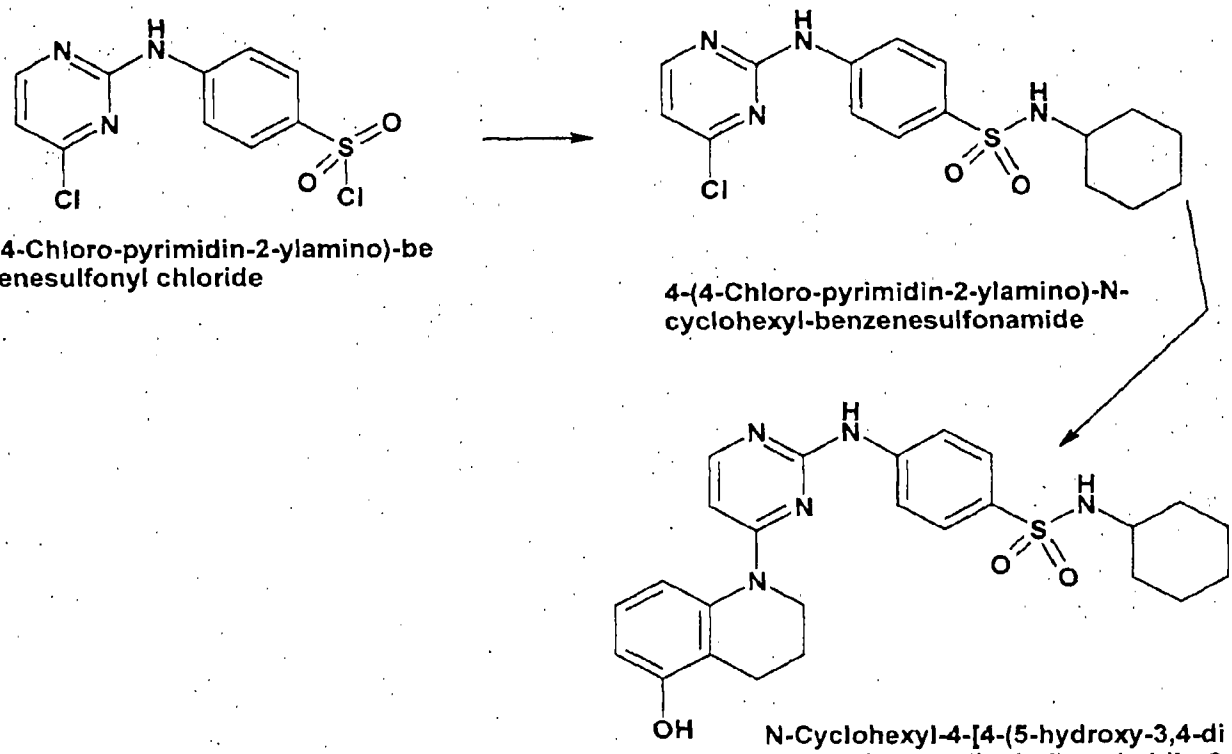
[00129] (4-Chloro-pyrimidine-2-yl)-phenyl-amine

[00130] 2-Phenylamino-pyrimidine-4-ol (1.309 g, 7 mmol) is suspended in 35 mL of acetonitrile and treated with 3.5 mL (14 mmol) of a 4 *m* solution of hydrochloric acid in dioxane (Aldrich) and 1.6 mL (17.5 mmol) phosphorous oxychloride under nitrogen and at room temperature. The mixture is heated under reflux for 3 hours, cooled and diluted with ethyl acetate. The resulting solution is washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate and evaporated. The residue is purified by flash chromatography on silica gel using ethyl acetate/hexane 2:8. The title compound is obtained in 86% yield (1.5 g): m.p. 134-135 °C; MS (ES+) *m/z* $(M + H)^{+1}$ 206.

[00131] 4-(4-Chloro-pyrimidine-2-ylamino)-benzenesulfonyl chloride

[00132] 3.2 mL (48 mmol) Chlorosulfonic acid are cooled to 0 °C under nitrogen. To this is added (4-chloro-pyrimidine-2-yl)-phenyl-amine (1.15 g, 5.6 mmol) in small portions under stirring. After complete addition, the mixture is stirred 15 minutes at 0 °C, 2 hours at room temperature and 15 minutes at 60 °C. The yellow solution is cooled and added slowly onto

100 g of crashed ice. After the ice has completely melted the solid is filtered off, washed with water and dried under vacuum. The title compound is obtained in 74% yield (1.26 g): m.p. 192-195 °C; MS (ES+) *m/z* $(M + H)^{+1}$ 300 (mass of the corresponding methyl sulfonate since the MS solution was made up in methanol).



4-(4-Chloro-pyrimidin-2-ylamino)-benzenesulfonyl chloride

4-(4-Chloro-pyrimidin-2-ylamino)-N-cyclohexyl-benzenesulfonamide

N-Cyclohexyl-4-[4-(5-hydroxy-3,4-dihydro-2H-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonamide

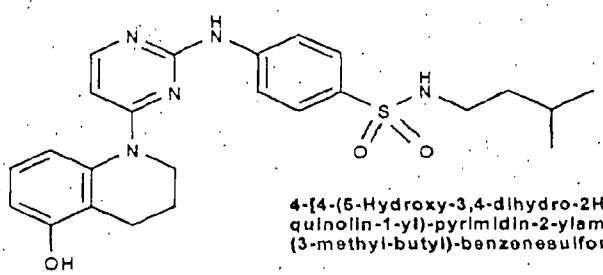
[00133] N-Cyclohexyl-4-[4-(5-hydroxy-3,4-dihydro-2H-quinolin-1-yl)-pyrimidine-2-ylamino]-benzenesulfonamide

[00134] A mixture of 560 mg (1.5 mmol) 4-(4-chloro-pyrimidine-2-ylamino)-N-cyclohexyl-benzenesulfonamide and 225 mg (1.52 mmol) 1,2,3,4-tetrahydro-quinoline-5-ol is heated without solvent in an oil bath for 15 minutes at 200 °C. The brown viscous mixture is cooled first to room temperature, then with dry ice, and the solidified material is pulverized. This solid is stirred with 5% citric acid solution, filtered, re-suspended in saturated sodium bicarbonate solution, filtered again and finally washed with water. This material is subjected to a flash chromatography on silica gel using ethyl acetate/hexane 8:2. Pure fractions are pooled and evaporated, stirred a few minutes in methanol, filtered, re-suspended in a mixture of toluene and diispropyl ether, filtered again and dried under vacuum. The title compound is obtained in 20% yield (150 mg): m.p. 236-238 °C; MS (ES+) *m/z* $(M + H)^{+1}$ 480.

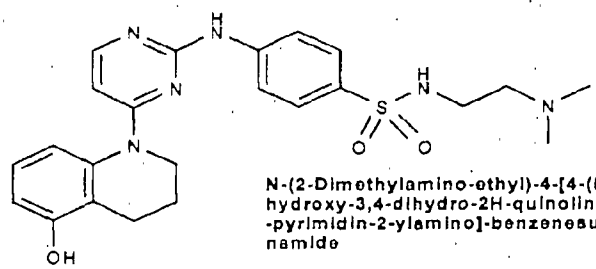
[00135] Starting material 4-(4-chloro-pyrimidine-2-ylamino)-N-cyclohexyl-benzenesulfonamide

[00136] 600 mg (2 mmol) 4-(4-Chloro-pyrimidine-2-ylamino)-benzenesulfonyl chloride are suspended in 60 mL of dichloromethane and treated at room temperature with 0.57 mL (5 mmol) cyclohexylamine. All the material goes slowly into solution and after stirring for about 15 minutes fine needles start to appear. The stirring is continued for a total of 2 hours then the mixture is diluted with dichloromethane and washed with 5% citric acid and brine. The organic phase is dried (Na_2SO_4) and evaporated. The title compound is obtained in 99% yield (706 mg): m.p. 202-204 °C; MS (ES+) *m/z* $(M + H)^{+1}$ 367.

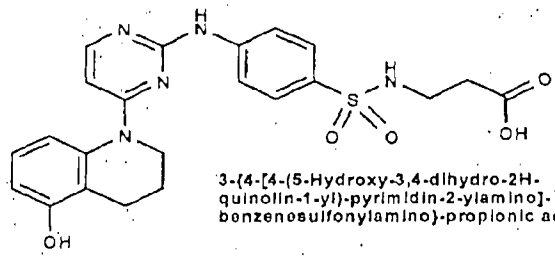
[00137] The following examples are synthesized using an analogous sequence as described for N-cyclohexyl-4-[4-(5-hydroxy-3,4-dihydro-2H-quinolin-1-yl)-pyrimidine-2-ylamino]-benzenesulfonamide:



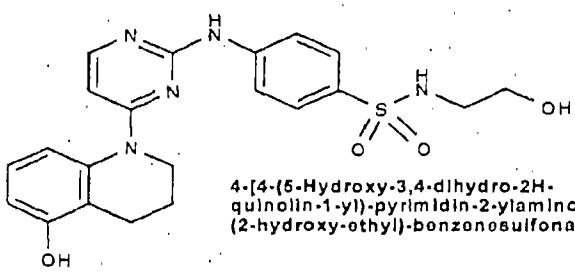
4-[4-(5-Hydroxy-3,4-dihydro-2H-quinolin-1-yl)-pyrimidin-2-ylamino]-N-(3-methyl-butyl)-benzenesulfonamide



N-(2-Dimethylamino-ethyl)-4-[4-(5-hydroxy-3,4-dihydro-2H-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonamide



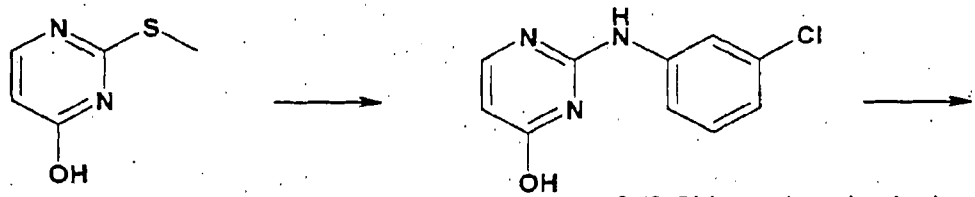
3-{4-[4-(5-Hydroxy-3,4-dihydro-2H-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonylamino}-propionic acid



4-[4-(5-Hydroxy-3,4-dihydro-2H-quinolin-1-yl)-pyrimidin-2-ylamino]-N-(2-hydroxy-ethyl)-benzenesulfonamide

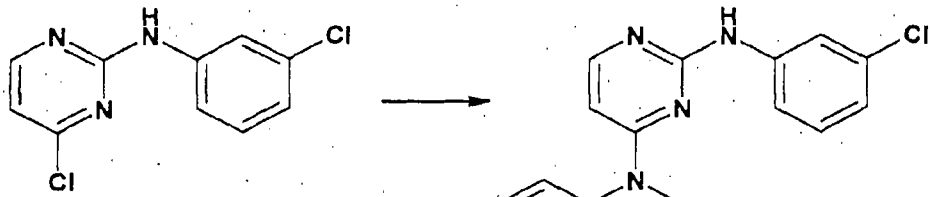
Comp. name	m.p. in °C	MS (ES+) *m/z* $(M + H)^{+1}$
4-[4-(5-Hydroxy-3,4-dihydro-2H-quinoline-1-yl)-pyrimidin-2-ylamino]-N-(3-methyl-butyl)-benzenesulfonamide	124-126	468
N-(2-Dimethylamino-ethyl)-4-[4-(5-hydroxy-3,4-dihydro-2H-quinoline-1-yl)-pyrimidin-2-ylamino]-benzenesulfonamide	175-177	469
3-{4-[4-(5-Hydroxy-3,4-dihydro-2H-quinoline-1-yl)-pyrimidin-2-ylamino]-benzenesulfonylamino}-propionic acid	217-219	470
4-[4-(5-Hydroxy-3,4-dihydro-2H-quinoline-1-yl)-pyrimidin-2-ylamino]-N-(2-hydroxy-ethyl)-benzenesulfonamide	242-245	442

[00138] (3-Chlorophenyl)-[4-(3,4-dihydro-2H-quinolin-1-yl)-pyrimidin-2-yl]-amine hydrochloride:



2-Methylsulfanyl-pyrimidin-4-ol

2-(3-Chloro-phenylamino)-pyrimidin-4-ol



(3-Chloro-phenyl)-(4-chloro-pyrimidin-2-yl)-amine

(3-Chloro-phenyl)-[4-(3,4-dihydro-2H-quinolin-1-yl)-pyrimidin-2-yl]-amine

[00139] 2-(3-Chloro-phenylamino)-pyrimidine-4-ol

[00140] 2-Methylsulfanyl-pyrimidine-4-ol (568 mg, 4 mmol) and 3-chloronaniline (0.47 mL, 4 mL) are mixed and heated for 30 minutes to 170 °C. The resulting solution is cooled and triturated with 0.1 m hydrochloric acid, filtered, washed with water and dried under vacuum. The title compound is obtained in 59% yield (520 mg): m.p. 250-252 °C; MS (ES+) *m/z* $(M + H)^{+1}$ 222.

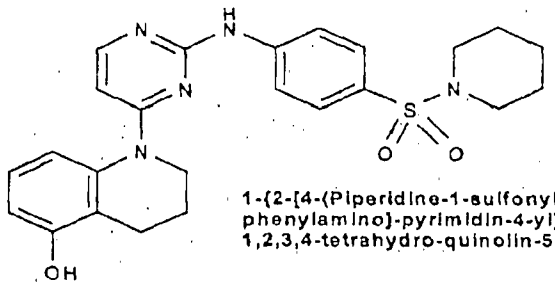
[00141] (3-Chloro-phenyl)-(4-chloro-pyrimidine-2-yl)-amine

[00142] 2-(3-Chloro-phenylamino)-pyrimidine-4-ol (444 mg, 2 mmol) is added in portions to 6 mL phosphorous oxychloride at room temperature. The mixture is heated to 70 °C for 1 hour, cooled and the excess phosphorous oxychloride evaporated under reduced pressure. The residue is dissolved in ethyl acetate washed with saturated sodium carbonate solution and brine, dried over sodium sulfate and evaporated. The title compound is obtained in 91% yield (440 mg): m.p. 112-114 °C; MS (ES+) *m/z* $(M + H)^{+1}$ 240,242.

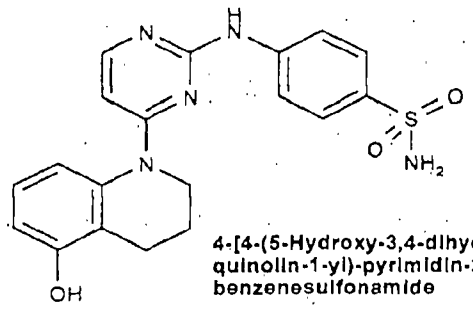
[00143] (3-Chloro-phenyl)-[4-(3,4-dihydro-2H-quinoline-1-yl)-pyrimidin-2-yl]-amine hydrochloride

[00144] (3-Chloro-phenyl)-(4-chloro-pyrimidine-2-yl)-amine (360 mg, 1.5 mmol) in 1 mL of dioxane is treated with 223 mg (1.5 mmol) 1,2,3,4-tetrahydro-quinoline-5-ol. The mixture is heated 2 hours at 80 °C and then 18 hours at 100 °C. The solvent was evaporated and the residue suspended in ethyl acetate/hexane 1:1 stirred for a few minutes and filtered. The title compound is obtained in 29% yield (150 mg): m.p. 250-252 °C; MS (ES+) *m/z* $(M + H)^{+1}$ 353.

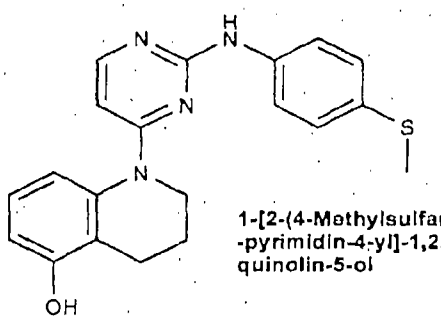
[00145] The following examples are synthesized using an analogous sequence as described for (3-Chlorophenyl)-[4-(3,4-dihydro-2H-quinolin-1-yl)-pyrimidin-2-yl]-amine hydrochloride. The compounds in the table are isolated as the free bases.



1-{2-[4-(Piperidine-1-sulfonyl)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-5-ol



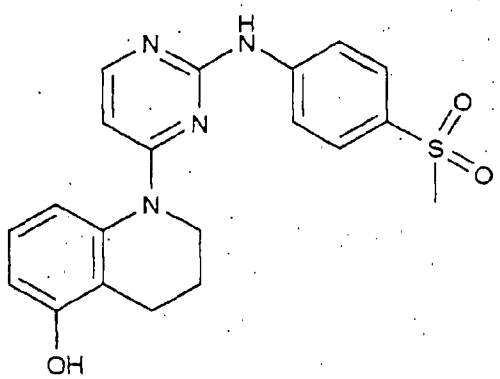
4-[4-(5-Hydroxy-3,4-dihydro-2H-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonamide



1-[2-(4-Methylsulfanyl-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-5-ol

Compound name	m.p. °C	MS (ES+) *m/z* $(M + H)^{+1}$
1-{2-[4-(Piperidine-1-sulfonyl)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-5-ol	126-128	466
4-[4-(5-Hydroxy-3,4-dihydro-2H-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonamide	155-158	398
1-[2-(4-Methylsulfanyl-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinoline-5-ol	190-192	365

[00146] 1-[2-(4-Methanesulfonyl-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-5-ol (oxidation product of 1-[2-(4-methylsulfanyl-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinoline-5-ol)



1-[2-(4-Methanesulfonyl-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-5-ol

[00147] 1-[2-(4-Methylsulfanyl-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinoline-5-ol (364 mg, 1 mmol) is suspended in 10 mL of dichloromethane at 0 °C. *m*-chloroperbenzoic acid (FLUKA 25800, 590 mg, 2.4 mmol) is added and the mixture stirred at 0 °C for 45 minutes. 100 mg of Na_2SO_3 are added and the reaction mixture is then partitioned between dichloromethane and water. The organic layer is separated and washed with saturated sodium bicarbonate, water and brine, dried over sodium sulfate and evaporated. The crude material is purified first by flash chromatography on silica gel using ethyl acetate and then by MPLC on a reverse phase column using an acetonitrile/water gradient containing 0.5% TFA. The title compound is obtained in 6% yield (25 mg): m.p. 242-245 °C; MS (ES+) *m/z* $(M + H)^{+1}$ 353.

[00148] Additional compounds within the scope of the present invention include the following:

1-[2-(3,4,5-trimethoxy-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-5-ol
4-[4-(5-hydroxy-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonamide
1-[2-(3,4,5-trimethoxy-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-6-ol

1-[2-(3,5-dimethoxy-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-5-ol

1-[2-(3,4,5-trimethoxy-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-7-ol

4-[4-(6-hydroxy-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-*N*-(2-hydroxy-ethyl)-benzenesulfonamide

{4-[4-(5-hydroxy-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonylamino}-acetic acid

1-[2-(3,5-dimethoxy-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-6-ol

4-[4-(6-hydroxy-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonamide

4-[4-(5-hydroxy-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-*N*-(2-hydroxy-ethyl)-3-methyl-benzenesulfonamide

1-[2-(3-chloro-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-5-ol

[4-(3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-yl]-(3,4,5-trimethoxy-phenyl)-amine

1-[2-(4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-7-ol

1-[2-(4-methylsulfanyl-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-5-ol

1-(2-phenylamino-pyrimidin-4-yl)-1,2,3,4-tetrahydro-quinolin-5-ol

1-[2-(3-hydroxy-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-5-ol

4-[4-(5-hydroxy-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-3-methyl-*N*-(3-methyl-butyl)-benzenesulfonamide

4-[4-(5-hydroxy-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-*N*-pyridin-4-ylmethyl-benzenesulfonamide

1-{2-[3-(2-imidazol-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-5-ol

1-{2-[3-(3-chloro-propoxy)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-6-ol

4-[4-(5-chloro-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonamide

1-{2-[3-(3-morpholin-4-yl-propoxy)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-5-ol

4-[4-(3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonamide

4-[4-(6-hydroxy-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-*N*-(3-methyl-butyl)-benzenesulfonamide

[4-(6-methyl-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-yl]-(3,4,5-trimethoxy-phenyl)-amine

1-{2-[3-(3-chloro-propoxy)-phenylamino]-pyrimidin-4-yl}-1,2,3,4-tetrahydro-quinolin-7-ol

[4-(7-methyl-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-yl]-(3,4,5-trimethoxy-phenyl)-amine

4-[4-(6-methyl-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-benzenesulfonamide

[4-(3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-yl]-(2,3-dimethoxy-benzyl)-amine

4-[4-(5-hydroxy-3,4-dihydro-2*H*-quinolin-1-yl)-6-methyl-pyrimidin-2-ylamino]-benzenesulfonamide

3-[4-(3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-phenol

4-[4-(6-fluoro-2-methyl-3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-2-ylamino]-*N*-(3-methyl-butyl)-benzenesulfonamide

1-[2-(3,4,5-trimethoxy-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-8-ol

[1-(2-phenylamino-pyrimidin-4-yl)-1,2,3,4-tetrahydro-quinolin-3-yl]-carbamic acid benzyl ester

1-[2-(4-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-quinolin-5-ol

[00149] Dry-filled capsules

[00150] 5000 capsules, each comprising as active ingredient 0.25 g of one of the compounds of formula I mentioned above, are prepared as follows:

[00151] Composition

active ingredient	1250 g
talcum	180 g
wheat starch	120 g
magnesium stearate	80 g
lactose	20 g

[00152] Preparation process

[00153] The mentioned substances are pulverized and forced through a sieve of 0.6 mm mesh size. 0.33 g portions of the mixture are introduced into gelatin capsules using a capsule-filling machine.

[00154] Soft capsules

[00155] 5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula (I) mentioned above, are prepared as follows:

[00156] Composition

active ingredient	250 g
PEG 400	1 L
Tween 80	1 L

[00157] Preparation process

[00158] The active ingredient is pulverized and suspended in PEG 400 (polyethylene glycol having an Mr of from approximately 380-420, Fluka, Switzerland) and Tween®80 (polyoxyethylene sorbitan monolaurate, Atlas Chem. Ind. Inc., USA, supplied by Fluka, Switzerland) and ground in a wet pulverizer to a particle size of approximately from 1-3 µm.

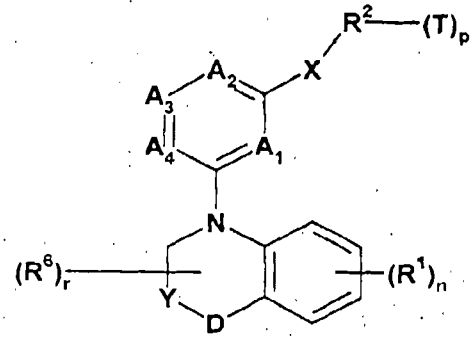
0.43 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

[00159] EQUIVALENTS

[00160] While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not to be limited to the disclosed embodiment, but on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

CLAIMS

1. A compound of formula (I)



or a pharmaceutically acceptable salt, ester or prodrug thereof for use as a pharmaceutical wherein

each of A_1, A_2, A_3, A_4 is independently selected from N or C-R^3 where R^3 represents H or a substituent moiety of C and where at least one of A_1, A_2 and A_4 is N;

X is a linking moiety selected from N-H, substituted amino, O or S;

R^1 is a substituent of the aromatic ring and n is an integer from 0 to 4;

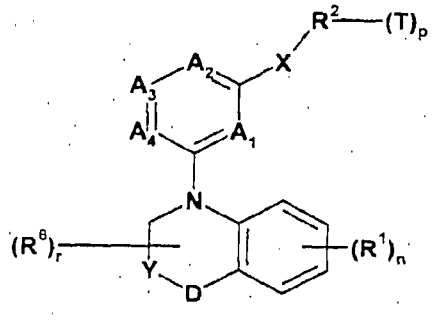
Y and D are independently selected from O, S, CH_2, NH, R^6-substituted C, or R^6-substituted N,

R^6 is a substituent of the ring which contains Y and D and r is an integer from 0 to the maximum number of available valencies of the ring;

R^2 is a substituted or unsubstituted moiety selected from hydrocarbyl and heterocyclic;

T is selected from H, halogen, O-R^9, S-R^8, SO-R^8 SO_2-R^8, SO_2-N(R^8)$_2$, SO_2-NR^{10} and SO_2-halogen, where R^8 is selected from hydrogen, substituted or unsubstituted alkyl, cycloalkyl, heterocyclyl or aryl; and R^9 is substituted or unsubstituted alkyl, cycloalkyl, or aryl, and NR^{10} represents a heterocyclic ring including the nitrogen; and p is an integer from 0 to 5.

2. A compound of formula (I)



or a pharmaceutically acceptable salt, ester or prodrug thereof

wherein

each of A_1, A_2, A_3, A_4 is independently selected from N or C-R^3 where R^3 represents H or a substituent moiety of C and where at least one of A_1, A_2 and A_4 is N;

X is a linking moiety selected from N-H, substituted amino, O or S;

R^1 is a substituent of the aromatic ring and n is an integer from 0 to 4;

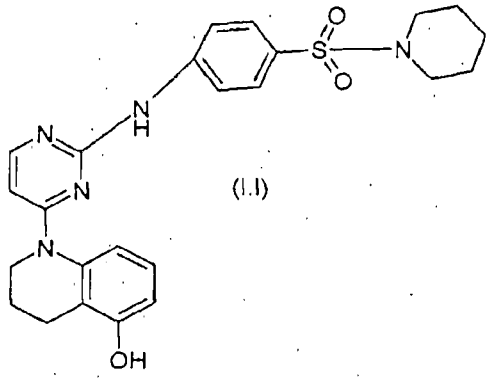
Y and D are independently selected from O, S, CH_2, NH, R^6-substituted C, or R^6-substituted N,

R^6 is a substituent of the ring which contains Y and D and r is an integer from 0 to the maximum number of available valencies of the ring;

R^2 is a substituted or unsubstituted moiety selected from hydrocarbyl and heterocyclic;

T is selected from H, halogen, O-R^8, S-R^8, SO-R^8 SO_2-R^8, SO_2-N(R^8)$_2$, SO_2-NR^{10} and SO_2-halogen, where R^8 is selected from hydrogen, substituted or unsubstituted alkyl, cycloalkyl, heterocyclyl or aryl; and R^9 is substituted or unsubstituted alkyl, cycloalkyl, or aryl, and NR^{10} represents a heterocyclic ring including the nitrogen; and p is an integer from 0 to 5

and wherein the compound is not:



(I.I)

3. A compound of claim 1 or 2 wherein A_1 and A_2 are N, and A_3 and A_4 are C-R^3.

4. A compound of claim 1, 2 or 3 wherein and A_3 and A_4 are C-H.

5. A compound of any of claims 1 to 4 wherein X is N-H.

6. A compound of any one of claims 1 to 5 wherein R^1, or each R^1 independently, is selected from OH, O-alkyl, SH, S-alkyl, halogen, substituted or unsubstituted amine, CF_3 and C_1-C_4 alkyl.

7. A compound as claimed in claim 6 wherein R^1 is OH.

8. A compound of any preceding claim wherein n is 1.

9. A compound of any preceding claim wherein Y is CH_2.

10. A compound of any preceding claim wherein D is CH_2.

11. A compound of any preceding claim wherein R^2 is selected from substituted or unsubstituted aliphatic, alicyclic, or aromatic moieties.

12. A compound of any preceding claim wherein R^2 is aromatic.

13. A compound as claimed in claim 12 wherein R^2 is selected from substituted or unsubstituted phenyl, imidazolyl, pyrrolyl, oxazolyl and isoxazolyl.

14. A compound as claimed in claim 12 wherein R^2 phenyl.

15. A compound as claimed in any preceding claim wherein p is 1.

16. A compound as claimed in claim 14 wherein p is 1 and T is located para- to the linking group X.

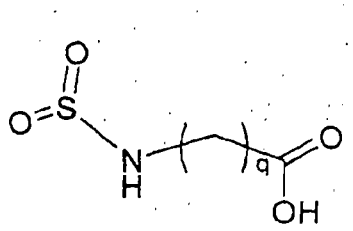
17. A compound as claimed in any preceding claim wherein T is selected from halogen, O-alkyl, O-alkyl-halogen, SO_2-R^8, SO_2-NHR^8, SO_2-NR^{10} and SO_2-halogen.

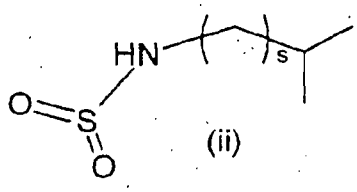
18. A compound as claimed in claim 17 wherein halogen is chlorine.

19. A compound as claimed in claim 17 wherein R^8 is substituted or unsubstituted alkyl or substituted or unsubstituted aryl.

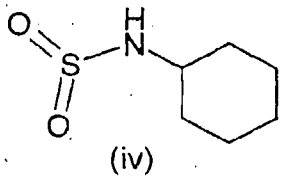
20. A compound as claimed in claim 17 wherein R^8 represents linear or branched alkyl, cycloalkyl, linear or branched halo-alkyl, alkoxy, carboxyalkyl, or alkylamino.

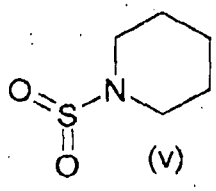
21. A compound as claimed in claim 17 wherein T is a moiety selected from the formulae (i) to (x):

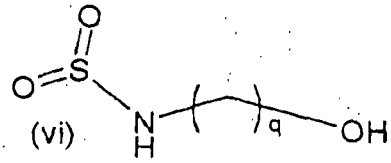

(i)

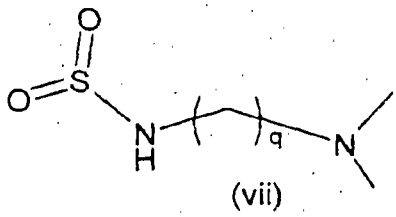

(ii)

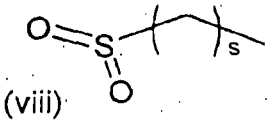

(iii)

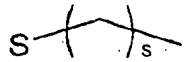

(iv)


(v)


(vi)


(vii)


(viii)

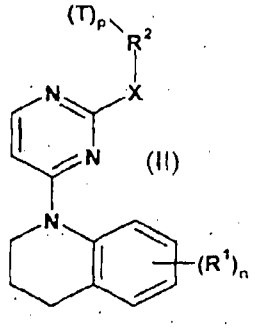

(ix)

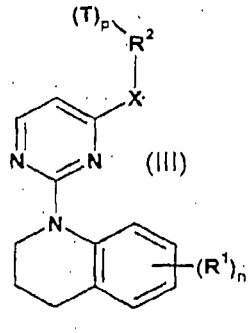

(x)

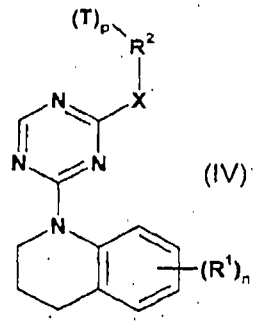
where q is an integer from 1 to 4 and s is an integer from 0 to 4

22. A compound as claimed in any preceding claim wherein r is 0.

23. A compound as claimed in claim 1 or 2 selected from compounds of the formulae (II), (III) and (IV):


(II)


(III)


(IV)

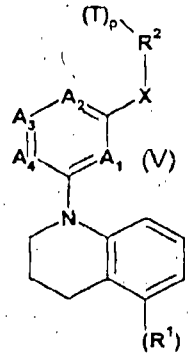
24. A compound as claimed in claim 23 wherein X is NH.

25. A compound as claimed in claim 23 or 24 wherein R^2 is phenyl.

26. A compound as claimed in claim 23, 24 or 25 wherein n is 1.

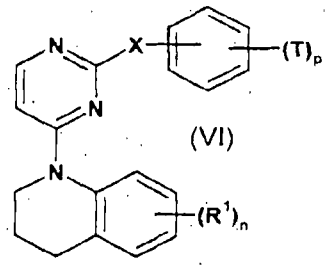
27. A compound as claimed in claim 23, 24, 25 or 26 wherein p is 1.

28. A compound as claimed in claim 1 or 2 of the formula (V):

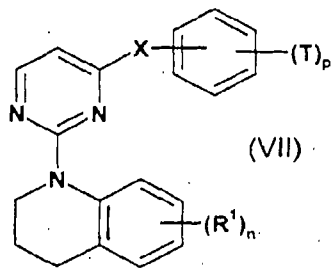


29. A compound as claimed in claim 28 wherein A_1 and A_2 are N, and A_3 and A_4 are C-R^3.

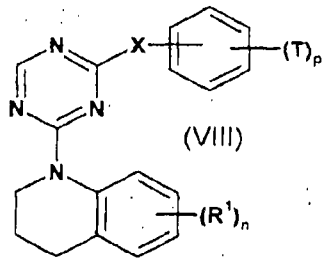
30. A compound as claimed in claim 1 or 2 selected from compounds for the formulae (VI), (VII) and (VIII):



(VI)



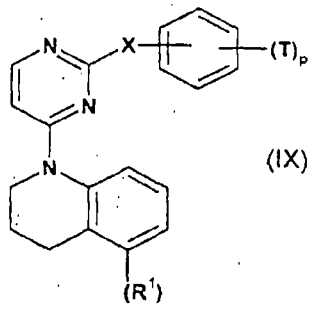
(VII)



(VIII)

31. A compound as claimed in claim 30 wherein n is 1.

32. A compound as claimed in claim 1 or 2 of the formula (IX)

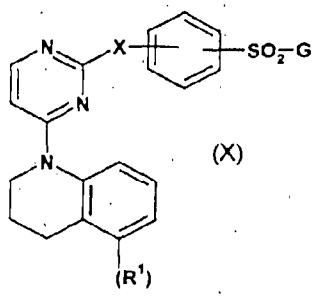


(IX)

33. A compound as claimed in claim 30, 31 or 32 wherein p is 1.

34. A compound as claimed in claim 30, 31, 32 or 33 wherein X is NH.

35. A compound as claimed in claim 1 or 2 of the formula (X)

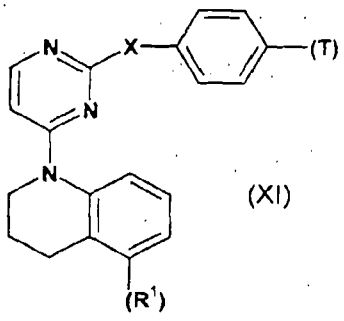


(X)

wherein G represents R^8, NHR^8 or NR^{10}.

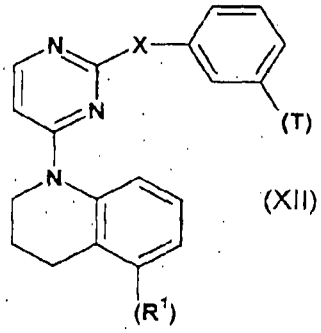
36. A compound as claimed in claim 35 wherein X is NH.

37. A compound as claimed in claim 1 or 2 of the formula (XI)



(XI)

38. A compound as claimed in claim 1 or 2 of the formula (XII)



(XII)

39. A compound as claimed in claim 38 wherein T is $O\text{-}R^9$.

40. A compound as claimed in claim 37, 38 or 39 wherein X is NH.

41. A compound as claimed in any preceding claim for use in the treatment of one or more of tyrosine and serine/threonine kinase and kinase-like dependant diseases.

42. The compound of any one of claims 1 to 40 for use in inhibiting IKK, PDGF-R, Kdr, c-Src, Her-1, Her-2, c-Kit, c-Abl, Ins-r, Tek, Flt-1, Flt-3, Flt-4, c-Abi and FGFR-1, Eph receptors (e.g. EphB4), CDK1, CDK2 and RET activity in a warm-blooded animal.

43. A compound as claimed in claim 42 for use in inhibiting RAF kinase activity in a warm blooded animal.

44. A compound as claimed in claim 41 wherein said diseases are selected from one or more of angiogenesis, cancer, tumour growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, neurotraumatic diseases, chronic neurodegeneration, pain, migraine or cardiac hypertrophy.

45. A compound of any preceding claim for use in the treatment of melanoma.

46. A compound of any preceding claim for use in the treatment of a disease characterized by an activated mutant B-RAF kinase.

47. The use of a compound of any of claims 1 to 40 for the manufacture of a medicament for use in the treatment of tyrosine and serine/threonine kinase and kinase-like-dependent diseases.

48. The use of a compound of any one of claims 1 to 40 for the manufacture of a medicament for use in the treatment of angiogenesis, cancer, tumour growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, neurotraumatic diseases, chronic neurodegeneration, pain, migraine or cardiac hypertrophy.

49. The use of a compound of any one of claims 1 to 40 for the manufacture of a medicament for use in the treatment of melanoma.

50. The use of a compound of any one of claims 1 to 40 for the manufacture of a medicament for use in the treatment of a disease characterized by an activated mutant B-RAF kinase.

51. The use as claimed in any one of claims 47 to 50 wherein said compound is administered alone.

52. The use as claimed in any one of claims 47 to 50 wherein said compound is administered in combination with at least one other anticancer agent.

53. The use as claimed in claim 52 wherein said other at least one other anticancer agent is chosen from protease inhibitors, epidermal growth factor receptor kinase inhibitors, vascular endothelial growth factor receptor kinase inhibitors, cytotoxic drugs, antimitotic agents, platinum coordination complexes, anti-tumor antibiotics, alkylating agents, endocrine agents, androgens, anti-androgens, estrogens, anti-estrogens, aromatase inhibitors, gonadotropin-releasing hormone agonists and somatostatin analogues and compounds that target an enzyme or receptor that is overexpressed and/or otherwise involved a specific metabolic pathway that is upregulated in the tumor cell, protein kinase inhibitors, threonine and tyrosine kinase inhibitors, epidermal growth factor receptor kinase inhibitors, vascular endothelial growth factor receptor kinase inhibitors, fibroblast growth factor inhibitors, insulin-like growth factor receptor inhibitors, platelet-derived growth factor receptor kinase inhibitors, methionine aminopeptidase inhibitors, proteasome inhibitors, cyclooxygenase inhibitors, and histone deacetylase inhibitors.

54. A pharmaceutical composition comprising a compound of any one of claims 1 to 40.

55. A pharmaceutical composition as claimed in claim 54 comprising from approximately 1% to approximately 95% of a compound of any one of claims 1 to 40.

56. A pharmaceutical composition of claim 54 or 55 comprising from approximately 20% to approximately 90% of a compound of any one of claims 1 to 40.

57. A pharmaceutical composition of claim 54, 55 or 56 comprising from approximately 5% to approximately 20% active ingredient.

58. A pharmaceutical composition of any one of claims 54 to 57 for administration by injection.

59. A pharmaceutical composition of claim 58 comprising a solution, suspension or dispersion of a compound of any one of claims 1 to 40.

60. A pharmaceutical composition of claim 58 or 59 additionally comprising a carrier.

61. A pharmaceutical composition of claim 60 wherein said carrier comprises mannitol.

62. A pharmaceutical composition of claim 59, 60 or 61 comprising a suspension in oil.

63. A pharmaceutical composition of any one of claims 54 to 57 for oral administration.

64. A pharmaceutical composition of claim 63 additionally comprising a solid carrier.

65. A pharmaceutical composition of claim 64 additionally comprising gelatin and a plasticiser.

66. A pharmaceutical composition of any one of claims 54 to 57 for rectal administration.

67. A pharmaceutical composition of claim 66 additionally comprising a suppository base.

68. A pharmaceutical composition comprising a compound of any of claims 1 to 40 and at least one anticancer agent.

69. The combination of the compound of any of claims 1 to 40 with at least one anticancer agent.

70. A pharmaceutical composition as claimed in claim 68 or a combination as claimed in claim 69 wherein the anticancer agent is selected from protease inhibitors, epidermal growth factor receptor kinase inhibitors, vascular endothelial growth factor receptor kinase inhibitors, cytotoxic drugs, antimitotic agents, platinum coordination complexes, anti-tumor antibiotics, alkylating agents, endocrine agents, androgens, anti-androgens, estrogens, anti-estrogens, aromatase inhibitors, gonadotropin-releasing hormone agonists and somatostatin analogues and compounds that target an enzyme or receptor that is overexpressed and/or otherwise involved a specific metabolic pathway that is upregulated in the tumor cell, protein kinase inhibitors, threonine and tyrosine kinase inhibitors, epidermal growth factor receptor kinase inhibitors, vascular endothelial growth factor receptor kinase inhibitors, fibroblast growth factor inhibitors, insulin-like growth factor receptor inhibitors, platelet-derived

growth factor receptor kinase inhibitors, methionine aminopeptidase inhibitors, proteasome inhibitors, cyclooxygenase inhibitors, and histone deacetylase inhibitors.

71. A method of treating a tyrosine, serine/threonine kinase or kinase-like-dependent disease comprising administering to a warm-blooded animal, for example a human, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 40.

72. A method of claim 71 which further comprises administering at the same time, or at a separate time, one or more anti-cancer agents.

73. A method of treating melanoma, which method comprises
(a) testing melanoma tissue from a patient to determine whether the melanoma tissue expresses mutant RAF kinase or overexpresses a wild-type RAF kinase, and
(b) treating the patient with an effective RAF kinase inhibiting amount of a RAF inhibiting compound as claimed in any one of claims 1 to 40 if the melanoma is found to overexpresses a wild type RAF kinase or express an activating mutant B-RAF kinase.

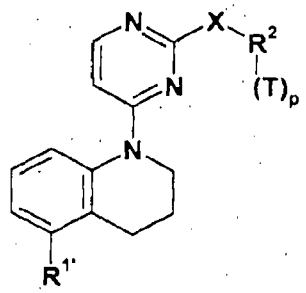
74. A method of treating melanoma, which method comprises
(a) testing melanoma tissue from a patient and determining whether the melanoma tissue overexpresses B-RAF kinase or C-RAF kinase activity, and
(b) treating the patient with an effective RAF kinase inhibiting amount of a RAF inhibiting compound as claimed in any one of claims 1 to 40 if the melanoma tissue is found to overexpress B-RAF kinase or C-RAF kinase activity.

75. A method of treating melanoma, which method comprises
(a) testing melanoma tissue from a patient and determining whether the melanoma tissue expresses mutant B-RAF kinase or C-RAF kinase activity, and
(b) treating the patient with an effective RAF kinase inhibiting amount of a RAF inhibiting compound as claimed in any one of claims 1 to 40 if the melanoma tissue is found to express mutant B-RAF kinase.

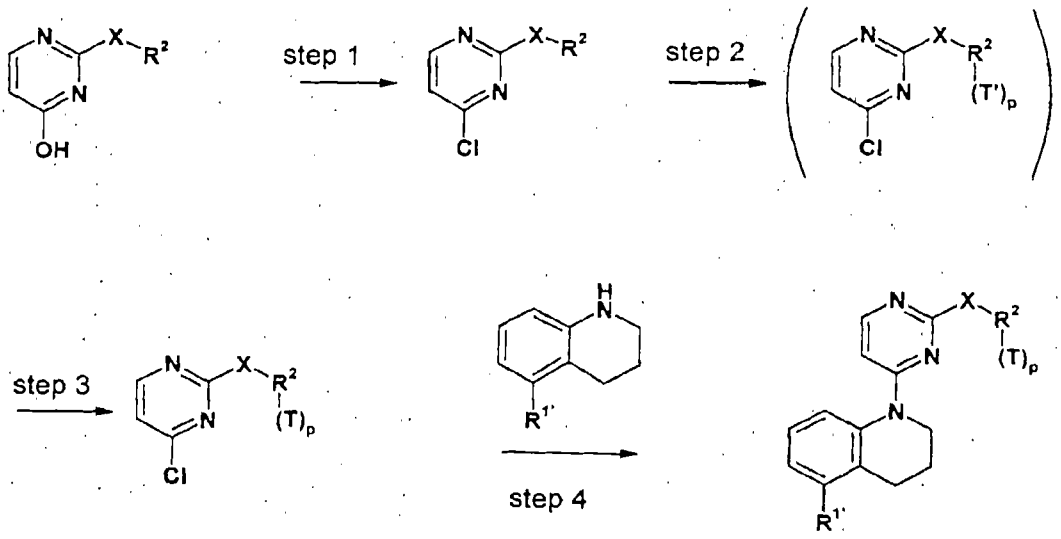
76. A method of treating a disease characterized by an activated mutant B-RAF kinase, which method comprises detecting a mutation in the B-RAF kinase gene or protein in a tissue sample from a patient and treating the patient with an effective B-RAF kinase inhibiting amount of a compound as claimed in any of claims 1 to 40.

77. A method of treating a patient having a disease characterized by excessive signaling through the MAP kinase signaling pathway, which comprises administering to the patient an effective RAF kinase inhibiting amount of a compound as claimed in any one of claims 1 to 40.

78. A process for the preparation of a compound of the formula



which process comprises the following reaction scheme:



where step 2 is optional and where carried out T' is a precursor of T, and $R^{1'}$ is a precursor of R^1 or is R^1 and X, R^1, R^2, T and P are as defined in claim 1.

79. A process as claimed in claim 78 wherein X is NH.

80. A process as claimed in claim 78 or 79 wherein R^2 is phenyl.

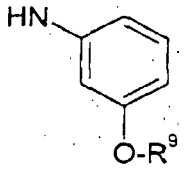
81. A process as claimed in claim 78, 79 or 80 wherein p is 1.

82. A process as claimed in any one of claims 78 to 81 wherein $R^{1'}$ is OH.

83. A process as claimed in any one of claims 78 to 82 wherein T represents SO_2-G where G represents R^8, NHR^8 or NR^{10} and R^8 and R^{10} are as defined in claim 1.

84. A process as claimed in any one of claims 78 to 83 wherein T represents O-R^9 where R^9 is as defined in claim 1.

85. A process as claimed in claim 84 wherein X-R^2-$(T)_p$ represents



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/006424

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D401/14 A61K31/506 A61P35/00 A61P25/00
A61P29/00

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

B. FIELDS SEARCHED

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

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, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/40215 A (PFIZER PROD INC [US]; BLUMENKOPF TODD ANDREW [US]; MUELLER EILEEN ELLI) 7 June 2001 (2001-06-07) all compounds on page 14 and on page 15, lines 1-12, 16-19, 21, 23-24 and 30-33; page 24, line 9 - page 26, line 21; claims; examples	1-85
X	WO 00/53595 A (ASTRAZENECA AB [SE]; BREAULT GLORIA ANNE [GB]; JAMES STEWART RUSSELL [) 14 September 2000 (2000-09-14) page 44, line 29 - page 48, line 2; claims 1,8-12; example 6	1-85

-/--

[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
19 July 2007	02/08/2007

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	Hanisch, Inken

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/006424

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/026130 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; IMBACH PATRICIA [CH]; ROE) 24 March 2005 (2005-03-24) page 23, line 44 - page 26, line 8; claims; compound 113	1-85
X	WO 02/056888 A (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; SCRIPPS RESEARCH) 25 July 2002 (2002-07-25) page 1, lines 16-24; page 4, line 4 - page 5, line 9; compound A; claims 7,10	1-41,44, 47,48, 51, 54-67,71
X	WO 92/05158 A (HOECHST AG [DE]) 2 April 1992 (1992-04-02) claims 1,2,5; examples 68,76,186	1-3,6,7, 9,11,15, 17-22
X	DE 32 33 604 A1 (HOECHST AG [DE]) 22 March 1984 (1984-03-22) example 17	1-3,6,7, 9-11,15, 17-22
X	EP 0 379 806 A2 (MITSUI PETROCHEMICAL IND [JP]; MITSUI PHARMACEUTICALS [JP]) 1 August 1990 (1990-08-01) claims 1,2,7-9; compounds 696,700,1124	1-7, 9-11,15, 17-24, 27,30, 33,34
X	OJEA V ET AL: "Synthesis of Fused Pyrido[2,3-d]pyrimidines by Thermal Isomerization of 4-Amino-5-vinylpyrimidines" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 5-6, 29 January 1998 (1998-01-29), pages 927-934, XP004106613 ISSN: 0040-4020 compounds 3b and 5b in scheme 1 and on pages 931, 932	1-3,6,7, 9-11,15, 17-22
X	WO 01/60816 A (AMGEN INC [US]) 23 August 2001 (2001-08-23) page 18, line 12 - page 19, line 6; page 21, line 7 - page 22, line 3; claims 1, 7-9,19-23; compounds 1-60; examples 19,20,25	1-85

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/006424

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/116388 A1 (ARMISTEAD DAVID M [US] ET AL ARMISTEAD DAVID M [US] ET AL) 17 June 2004 (2004-06-17) paragraphs [0223], [0227]-[0228]; claims 1,11,20,22-31; examples 36,49; compounds 298,326,498,518,535,567,582,609,612,635, 639,643-645	1,2, 5-31, 41-85
X	US 5 998 436 A (YAZAKI AKIRA [JP] ET AL) 7 December 1999 (1999-12-07) example 60	1,2,5-7, 11,15, 17-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/006424

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 claims 71-77 are 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/US2007/006424

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0140215 A	07-06-2001	AT	315036 T	15-02-2006
		AU	1047601 A	12-06-2001
		BG	106695 A	29-12-2002
		BR	0015995 A	06-08-2002
		CA	2392971 A1	07-06-2001
		CN	1402720 A	12-03-2003
		CZ	20021703 A3	18-06-2003
		DE	60025385 T2	24-08-2006
		EE	200200275 A	15-10-2003
		EP	1242403 A1	25-09-2002
		ES	2253266 T3	01-06-2006
		HU	0203300 A2	28-02-2003
		IS	6339 A	12-04-2002
		JP	2003515602 T	07-05-2003
		MA	26846 A1	20-12-2004
		MX	PA02005350 A	11-12-2002
		NO	20022557 A	29-05-2002
		OA	12097 A	04-05-2006
		PL	355946 A1	31-05-2004
WO 0053595 A	14-09-2000	AT	241617 T	15-06-2003
		AU	754967 B2	28-11-2002
		AU	2818700 A	28-09-2000
		BR	0008770 A	08-01-2002
		CA	2366668 A1	14-09-2000
		CN	1349528 A	15-05-2002
		DE	60003001 D1	03-07-2003
		DE	60003001 T2	06-05-2004
		DK	1161428 T3	15-09-2003
		EP	1161428 A1	12-12-2001
		ES	2200824 T3	16-03-2004
		JP	2002539120 T	19-11-2002
		MX	PA01008960 A	24-04-2002
		NO	20014317 A	01-11-2001
		NZ	513893 A	26-03-2004
		PT	1161428 T	31-10-2003
		US	6716831 B1	06-04-2004
		ZA	200107252 A	02-12-2002
WO 2005026130 A	24-03-2005	AU	2004272288 A1	24-03-2005
		BR	PI0414544 A	07-11-2006
		CA	2538413 A1	24-03-2005
		CN	1852900 A	25-10-2006
		EP	1663992 A1	07-06-2006
		JP	2007505858 T	15-03-2007
		MX	PA06003054 A	31-05-2006
WO 02056888 A	25-07-2002	AU	2002237274 A1	30-07-2002
		US	2002132823 A1	19-09-2002
WO 9205158 A	02-04-1992	DE	4029648 A1	26-03-1992
		ZA	9107428 A	29-04-1992
DE 3233604 A1	22-03-1984	NONE		
EP 0379806 A2	01-08-1990	AT	136542 T	15-04-1996
		AU	629595 B2	08-10-1992
		AU	4732989 A	05-07-1990

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/006424

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0379806 A2		CA 2006944 A1	29-06-1990
		CN 1045390 A	19-09-1990
		DE 68926232 D1	15-05-1996
		DE 68926232 T2	17-10-1996
		HU 52769 A2	28-08-1990
		US 5147876 A	15-09-1992
WO 0160816 A	23-08-2001	AU 3704101 A	27-08-2001
		CA 2400447 A1	23-08-2001
		CN 1429222 A	09-07-2003
		HU 0301117 A2	29-12-2003
		ZA 200206386 A	26-11-2003
US 2004116388 A1	17-06-2004	NONE	
US 5998436 A	07-12-1999	AT 210129 T	15-12-2001
		AT 241601 T	15-06-2003
		AT 222906 T	15-09-2002
		AU 707565 B2	15-07-1999
		AU 7001696 A	09-04-1997
		BR 9610485 A	27-07-1999
		CA 2232728 A1	27-03-1997
		CN 1201459 A	09-12-1998
		CN 1258672 A	05-07-2000
		CN 1258674 A	05-07-2000
		DE 69617750 D1	17-01-2002
		DE 69617750 T2	08-08-2002
		DE 69623358 D1	02-10-2002
		DE 69623358 T2	08-05-2003
		DE 69628466 D1	03-07-2003
		DE 69628466 T2	01-04-2004
		DK 911327 T3	02-04-2002
		DK 0952151 T3	22-09-2003
		DK 0992501 T3	28-10-2002
		EP 0911327 A1	28-04-1999
		ES 2169811 T3	16-07-2002
		ES 2200439 T3	01-03-2004
		ES 2183473 T3	16-03-2003
		HK 1028032 A1	25-06-2004
		HK 1016602 A1	29-08-2003
		HU 9902714 A2	28-12-1999
		HU 225225 B1	28-08-2006
		WO 9711068 A1	27-03-1997
		JP 3103380 B2	30-10-2000
		PT 911327 T	31-05-2002
		PT 952151 T	31-10-2003
		PT 992501 T	31-01-2003
		US 6133284 A	17-10-2000
		US 6156903 A	05-12-2000