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HETEROCYCLIC COMPOUNDS

The present invention relates to a series of substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to quinazoline and pyridopyrimidine derivatives which exhibit protein tyrosine kinase inhibition.

Protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth and differentiation (A.F. Wilks, Progress in Growth Factor Research, 1990, 2, 97-111; S.A. Courtneidge, Dev. Supp.l, 1993, 57-64; J.A. Cooper, Semin. Cell Biol., 1994, 5(6), 377-387; R.F. Paulson, Semin. Immunol., 1995, 7(4), 267-277; A.C. Chan, Curr. Opin. Immunol., 1996, 8(3), 394-401). Protein tyrosine kinases can be broadly classified as receptor (e.g. EGFr, c-erbB-2, c-met, tie-2, PDGFr, FGFr) or non-receptor (e.g. c-src, lck, zap70) kinases. Inappropriate or uncontrolled activation of many of these kinase, i.e. aberrant protein tyrosine kinase activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth.

Aberrant activity of protein tyrosine kinases, such as c-erbB-2, c-src, c-met, EGFr and PDGFr have been implicated in human malignancies. Elevated EGFr activity has, for example, been implicated in non-small cell lung, bladder and head and neck cancers, and increased c-erbB-2 activity in breast, ovarian, gastric and pancreatic cancers. Inhibition of protein tyrosine kinases should therefore provide a treatment for tumours such as those outlined above.

Aberrant protein tyrosine kinase activity has also been implicated in a variety of other disorders: psoriasis, (Dvir et al, J.Cell.Biol; 1991, 113, 857-865), fibrosis, atherosclerosis, restenosis, (Buchdunger et al, Proc.Natl.Acad.Sci. USA; 1991, 92, 2258-2262), auto-immune disease, allergy, asthma, transplantation rejection (Klausner and Samelson, Cell; 1991, 64, 875-878), inflammation (Berkois, Blood; 1992, 79(9), 2446-2454), thrombosis (Salari et al, FEBS; 1990, 263(1), 104-108) and nervous system diseases (Ohmichi et al, Biochemistry, 1992, 31, 4034-4039). Inhibitors of the specific protein tyrosine kinases involved in these diseases eg PDGF-R in restenosis and EGF-R in psoriasis, should lead to novel therapies for such disorders. P56lck and zap 70 are indicated in disease conditions in which T

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cells are hyperactive e.g. rheumatoid arthritis, autoimmune disease, allergy, asthma and graft rejection. The process of angiogenesis has been associated with a number of disease states (e.g. tumourogenesis, psoriasis, rheumatoid arthritis) and this has been shown to be controlled through the action of a number of receptor tyrosine kinases (L.K. Shawver, DDT, 1997, 2(2), 50-63).

It is therefore a general object of the present invention to provide compounds suitable for the treatment of disorders mediated by protein tyrosine kinase activity, and in particular treatment of the above mentioned disorders.

In addition to the treatment of tumours, the present invention envisages that other disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition, including preferential inhibition, of the appropriate protein tyrosine kinase activity.

Broad spectrum inhibition of protein tyrosine kinase may not always provide optimal treatment of, for example tumours, and could in certain cases even be detrimental to subjects since protein tyrosine kinases provide an essential role in the normal regulation of cell growth.

It is another object of the present invention to provide compounds which preferentially inhibit protein tyrosine kinases, such as EGFr, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFr, c-src, lck, Zap70, and fyn. There is also perceived to be a benefit in the preferential inhibition involving small groups of protein tyrosine kinases, for example groups including two or more of c-erbB-2, c-erbB-4, EGF-R, lck and zap70.

A further object of the present invention is to provide compounds useful in the treatment of protein tyrosine kinase related diseases which minimise undesirable side-effects in the recipient.

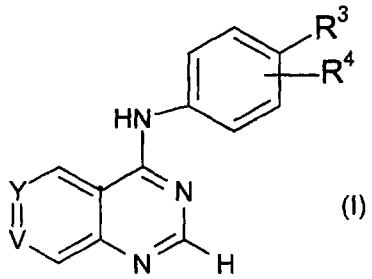
The present invention relates to heterocyclic compounds which may be used to treat disorders mediated by protein tyrosine kinases and in particular have anti-cancer properties. More particularly, the compounds of the present invention are potent inhibitors of protein tyrosine kinases such as such as EGFr, c-erbB-2, c-erbB-4, c-

met, tie-2, PDGFr, c-src, lck, Zap70, and fyn, thereby allowing clinical management of particular diseased tissues.

The present invention envisages, in particular, the treatment of human malignancies, for example breast, non-small cell lung, ovary, stomach, and pancreatic tumours, especially those driven by EGF-R or erbB-2, using the compounds of the present invention. For example, the invention includes compounds which are highly active against the c-erbB-2 protein tyrosine kinase often in preference to the EGF receptor kinase hence allowing treatment of c-erbB-2 driven tumours. However, the invention also includes compounds which are highly active against both c-erbB-2 and EGF-R receptor kinases hence allowing treatment of a broader range of tumours.

More particularly, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity in a relatively selective manner, thereby minimising potential side effects.

Accordingly, the present invention provides a compound of formula (I)



(I)

or a salt or solvate thereof;

wherein

Y is CR^1 and V is N;
or Y is CR^1 and V is CR^2;

R^1 represents a group $CH_3SO_2CH_2CH_2NHCH_2$-Ar-, wherein Ar is selected from furan and thiazole, each of which may optionally be substituted by one or two halo, C_{1-4} alkyl or C_{1-4} alkoxy groups;

R^2 is hydrogen or C_{1-4} alkoxy; or R^2 is halo;

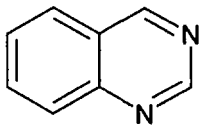
R^3 is selected from a group comprising benzyl, halo-, dihalo- and trihalobenzyl, benzoyl, pyridylmethyl, pyridylmethoxy, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl;

R^4 is halo or C_{1-4} alkoxy or is not present;

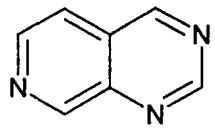
wherein
either (a) R^3 represents 3-fluorobenzyloxy;
and/or (b) R^4 is selected from halo and is substituted in the 3-position of the phenyl ring;
and halo represents fluoro, chloro or bromo.

Solvates of the compounds of formula (I) are also included within the scope of the present invention.

The definitions for Y and V thus give rise to a number of possible basic ring systems for the compounds of formula (I). In particular the compounds may contain the following basic ring systems:



(2)



(6)

It will be seen that for compounds containing the basic ring system (2) the group R^1 will be at the 6- position; such compounds are of particular interest in the context of c-erbB-2 activity.

Alkyl groups containing three or more carbon atoms may be straight, branched or cyclised; preferably they are straight or branched. References to a specific alkyl group such as "butyl" is intended to refer to the straight chain (n-) isomer only. References to other generic terms such as alkoxy, alkylamino etc. are to be interpreted analogously.

Suitable values for the various groups listed above within the definitions for R^1, R^2, R^4 and R^5 are as follows:
halo is fluoro, chloro or bromo, more preferably fluoro or chloro;
C_{1-4} alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl; preferably it is methyl, ethyl, propyl, isopropyl or butyl, more preferably methyl;
C_{1-4} alkoxy is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy; preferably it is methoxy, ethoxy, propoxy, isopropoxy or butoxy; more preferably it is methoxy.

In an especially preferred embodiment Y is CR^1 and V is CR^2 (ring system (2) above).

In a further especially preferred embodiment Y is CR^1 and V is N (ring system (6) above).

In a preferred embodiment R^2 represents hydrogen or C_{1-4} alkoxy.

In a more preferred embodiment R^2 represents hydrogen or methoxy.

In a further preferred embodiment R^2 represents halo; more preferred R^2 is fluoro.

In a preferred embodiment the group Ar is substituted by one halo, C_{1-4} alkyl or C_{1-4} alkoxy group.

In a more preferred embodiment the group Ar is substituted by a C_{1-4} alkyl group.

In a further more preferred embodiment the group Ar does not carry any optional substituents.

In a most preferred embodiment Ar represents unsubstituted furan or thiazole.

The side chain $CH_3SO_2CH_2CH_2NHCH_2$ may be linked to any suitable position of the group Ar. Similarly, the group R^1 may be linked to the carbon atom carrying it from any suitable position of the group Ar.

In a preferred embodiment, when Ar represents furan the side chain $CH_3SO_2CH_2CH_2NHCH_2$ is in the 4-position of the furan ring and the link to the carbon atom carrying the group R^1 is from the 2-position of the furan ring.

In another preferred embodiment, when Ar represents furan the side chain $CH_3SO_2CH_2CH_2NHCH_2$ is in the 3-position of the furan ring and the link to the carbon atom carrying the group R^1 is from the 2-position of the furan ring.

In a most preferred embodiment, when Ar represents furan the side chain $CH_3SO_2CH_2CH_2NHCH_2$ is in the 5-position of the furan ring and the link to the carbon atom carrying the group R^1 is from the 2-position of the furan ring.

In a further most preferred embodiment, when Ar represents thiazole the side chain $CH_3SO_2CH_2CH_2NHCH_2$ is in the 2-position of the thiazole ring and the link to the carbon atom carrying the group R^1 is from the 4-position of the thiazole ring.

In a preferred embodiment R^3 represents benzyl, pyridylmethyl, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl.

In a more preferred embodiment R^3 represents benzyloxy, fluorobenzyloxy (especially 3-fluorobenzyloxy), benzyl, phenoxy and benzenesulphonyl.

In a further more preferred embodiment R^3 represents bromobenzyloxy (especially 3-bromobenzyloxy).

In a further preferred embodiment R^4 is not present.

In a further preferred embodiment R^4 is selected from halo or C_{1-4} alkoxy; especially chloro, fluoro or methoxy.

In a more preferred embodiment R^4 represents halo, especially 3-fluoro.

In an especially preferred embodiment the phenyl ring together with R^4 represents methoxyphenyl, fluorophenyl, or chlorophenyl.

In a more especially preferred embodiment the phenyl ring together with R^4 represents methoxyphenyl or fluorophenyl.

In an especially preferred embodiment the phenyl ring together with the substituent(s) R^3 and R^4 represents (3-fluorobenzyloxy)phenyl.

In another especially preferred embodiment the phenyl ring together with the substituent(s) R^3 and R^4 represents (3-fluorobenzyloxy)-3-methoxyphenyl.

In a more especially preferred embodiment the phenyl ring together with the substituent(s) R^3 and R^4 represents 3-fluorobenzyloxy-3-chlorophenyl, benzyloxy-3-chlorophenyl, (benzyloxy)-3-fluorophenyl, or (3-fluorobenzyloxy)-3-fluorophenyl.

Preferred compounds of the present invention include:
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
N-{4-[(3-Fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-{4-[(3-Fluorobenzyl)oxy]-3-methoxyphenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-{4-[(3-Fluorobenzyl)oxy]-3-methoxyphenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-{4-[(3-Fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(Benzyloxy)-3-fluorophenyl]-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-(3-Fluoro-4-benzyloxyphenyl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-(3-Chloro-4-benzyloxyphenyl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts thereof.

Other preferred compounds of the present invention include the following (in groups denoted hereafter as Lists 1 to 9):

List 1
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;

List 2
(4-Benzyloxy-3-chlorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-3-bromophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-bromophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-fluorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy-3-fluorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

List 3
(4-Benzyloxy-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-fluorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-fluorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

List 4
(4-Benzyloxy-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine
(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;

List 5
(4-Benzyloxy-3-bromophenyl)-(6-(5-((2methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy-3-bromophenyl)-(6-(5-((2methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

List 6
N-[4-(Benzyloxy)-3-chlorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-Benzyloxy-3-bromophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-bromophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-Benzyloxy-3-fluorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-fluorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

List 7
N-[4-(Benzyloxy)-3-chlorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine
N-[4-Benzyloxy-3-bromophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine
N-[4-(3-Fluoro-benzyloxy)-3-bromophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine
N-[4-Benzyloxy-3-fluorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine
N-[4-(3-Fluoro-benzyloxy)-3-fluorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

List 8

N-[4-(Benzyloxy)-3-chlorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-bromophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-bromophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-fluorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-fluorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

List 9
N-[4-(Benzyloxy)-3-chlorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-bromophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-bromophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-fluorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-fluorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Particularly preferred compounds of the present invention include:
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

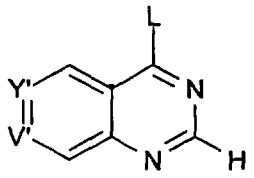
N-{4-[(3-Fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-(3-Fluoro-4-benzyloxyphenyl)-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine;
N-(3-Chloro-4-benzyloxyphenyl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine;
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism). The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen in the compound of formula (I). The therapeutic activity resides in the moiety derived from the compound of the invention as defined herein and the identity of the other component is of less importance although for therapeutic and prophylactic purposes it is, preferably, pharmaceutically acceptable to the patient. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic, acids.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

(a) the reaction of a compound of formula (II)



(II)

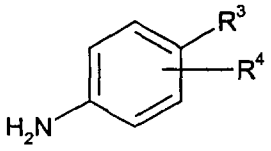
wherein

Y' is CL' and V' is N;

or Y' is CL' and V' is CR^2;

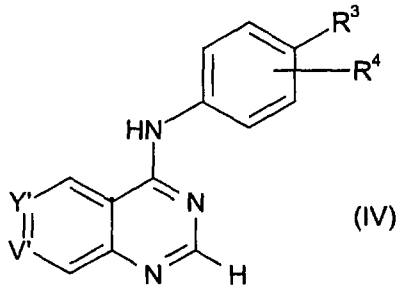
wherein R^2 is as defined above, and L and L' are suitable leaving groups,

with a compound of formula (III)



(III)

wherein R^3 and R^4 are as defined above, to prepare a compound of formula (IV)

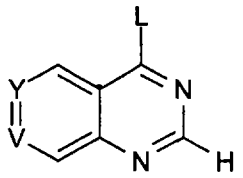


(IV)

and subsequently (b) reaction with appropriate reagent(s) to substitute the group R^1 by replacement of the leaving group L'; and, if desired, (c) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

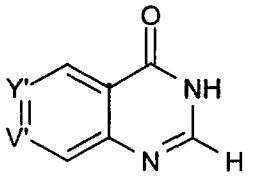
Alternatively, the compound of formula (II) as defined above is reacted with the appropriate reagents to substitute the group R^1 by replacement of the leaving group L' and then the product thereby obtained (of formula (V) below) is reacted with the compound of formula (III) as defined above, followed, if desired, by conversion of the compound of formula (I) thereby obtained into another compound of formula (I).

In a variant of this alternative the compound of formula (V)



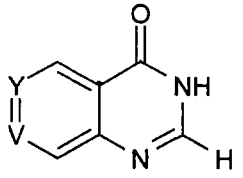
(V)

wherein Y, V and L are as defined above, may be prepared by the reaction of a compound of formula (VI)



(VI)

wherein V' and Y' are as defined above, with appropriate reagents to substitute the group R^1 for the leaving group L' to prepare a compound of formula (VII)



(VII)

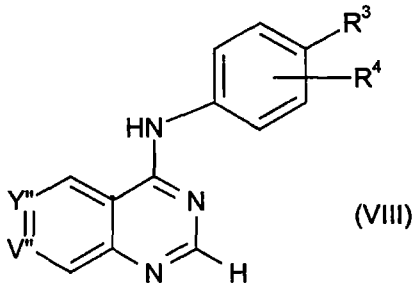
and subsequent reaction to incorporate the leaving group L. For example, a chloro leaving group can be incorporated by reaction of a corresponding 3,4-dihydropyrimidone with carbon tetrachloride/triphenylphosphine in an appropriate solvent.

The group R^1 may, therefore, be substituted onto the basic ring system by replacement of a suitable leaving group. This may, for example, be carried out by reaction of the corresponding aryl or heteroaryl stannane derivative with the

corresponding compound of formula (IV) carrying the leaving group L' in the appropriate position on the ring.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

(a) reacting a compound of formula (IV) as defined above with appropriate reagent(s) to prepare a compound of formula (VIII)



(VIII)

wherein R^3 and R^4 are as defined above;

Y" is CT and V" is N;

or Y" is CT and V" is CR^2;

wherein R^2 is as defined above and T is an appropriately functionalised group;

and (b) subsequently converting the group T into the group R^1 by means of appropriate reagent(s); and, if desired, (c) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

In one alternative, the group T would represent a group Ar as defined above carrying a formyl group (CHO).

Where T represents a group Ar carrying a formyl group the compound (of formula (VIIIa)) may be suitably prepared from the corresponding dioxolanyl substituted compound (of formula (VIIIb)), for example by acid hydrolysis. The dioxolanyl substituted compound may be prepared by reaction of a compound of formula (IV) with an appropriate reagent to substitute the relevant leaving group with the substituent carrying the dioxolanyl ring. This reagent could, for example, be an appropriate heteroaryl stannane derivative.

Therefore a suitable process may comprise reaction of a compound of formula (VIIIa) in which T is a group Ar carrying a formyl substituent (i.e. a -CHO group) with a compound of formula $CH_3SO_2CH_2CH_2NH_2$. The reaction preferably involves a reductive amination by means of an appropriate reducing agent, for example sodium triacetoxyborohydride.

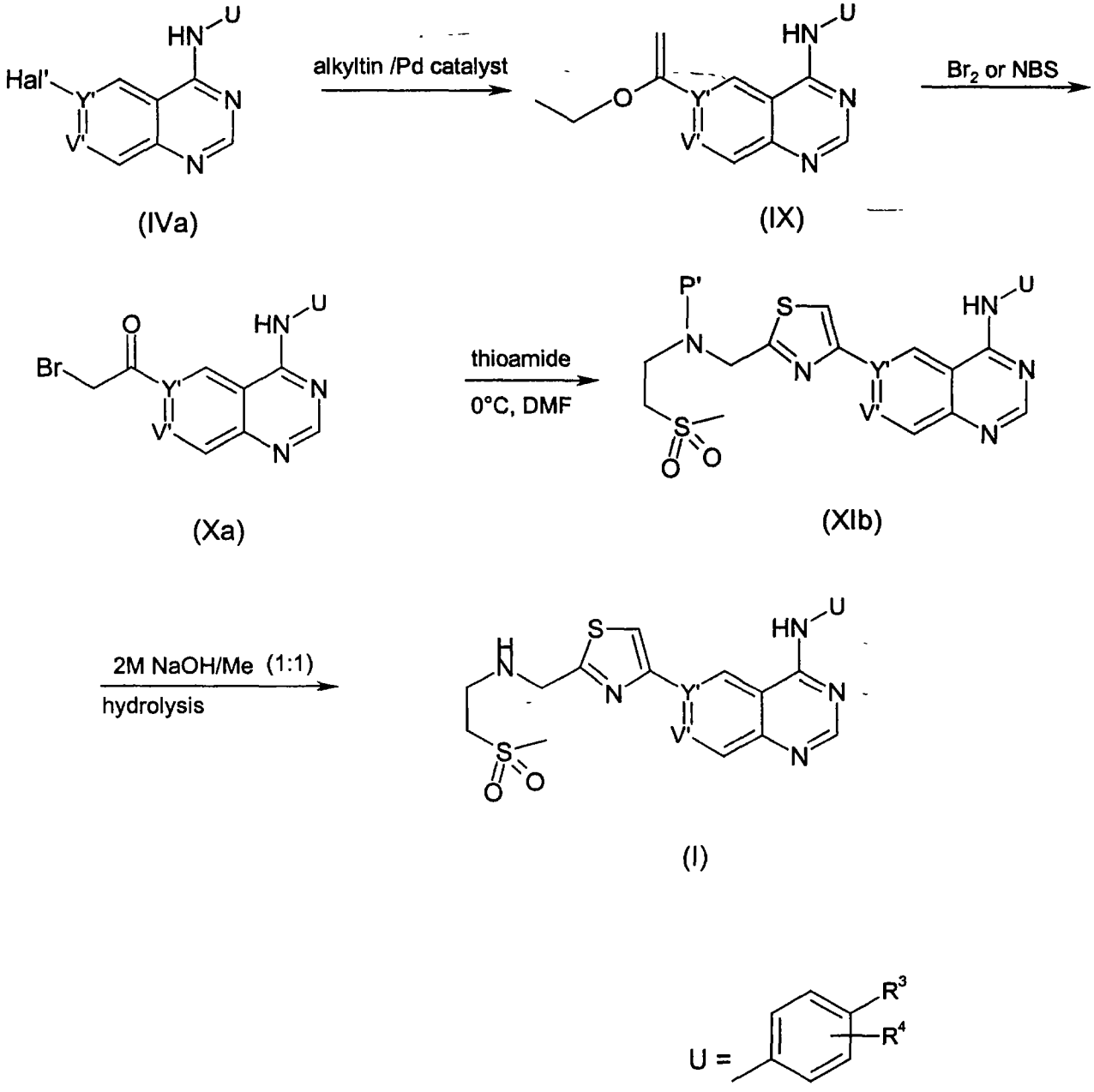
Alternatively, another suitable process may comprise oxidation of a compound of formula (VIIIc) in which T is a group Ar carrying a substituent of formula $CH_3SCH_2CH_2NHCH_2$ or $CH_3SOCH_2CH_2NHCH_2$. Suitable methods for the oxidation to the desired compound of formula (I) will be well known to the person skilled in the art but include, for example, reaction with an organic peroxide, such as peracetic acid or metachlorobenzoic acid, or reaction with an inorganic oxidising agent, such as OXONE®. The compound of formula (VIIIc) in which T is a group Ar carrying a substituent of formula $CH_3SCH_2CH_2NHCH_2$ or $CH_3SOCH_2CH_2NHCH_2$ may be prepared by an analogous reaction to that described above, namely reaction of a compound of formula (VIIIa) in which T is a group Ar carrying a formyl substituent (i.e. a -CHO group) with a compound of formula $CH_3SCH_2CH_2NH_2$ or $CH_3SOCH_2CH_2NH_2$ respectively.

Alternatively, an analogous scheme to those described above could be used wherein the substitution of the group R^1 onto the basic ring system occurs prior to the coupling reaction with the compound of formula (III).

According to a further alternative process the group T is converted into the group R^1 by a *de novo* synthesis of a substituted heterocyclic system using appropriate agents. Such a process would involve standard synthetic methodology known to the person skilled in the art for building up the heterocylic ring system.

For example, T could represent a haloketone group as shown in the compound of formula (IX) in scheme 1 below which, when coupled with an appropriate N-protected thioamide [compound of formula (XI) in scheme 2], would result in the formation of an N-protected amino-substituted thiazole system of formula (X).

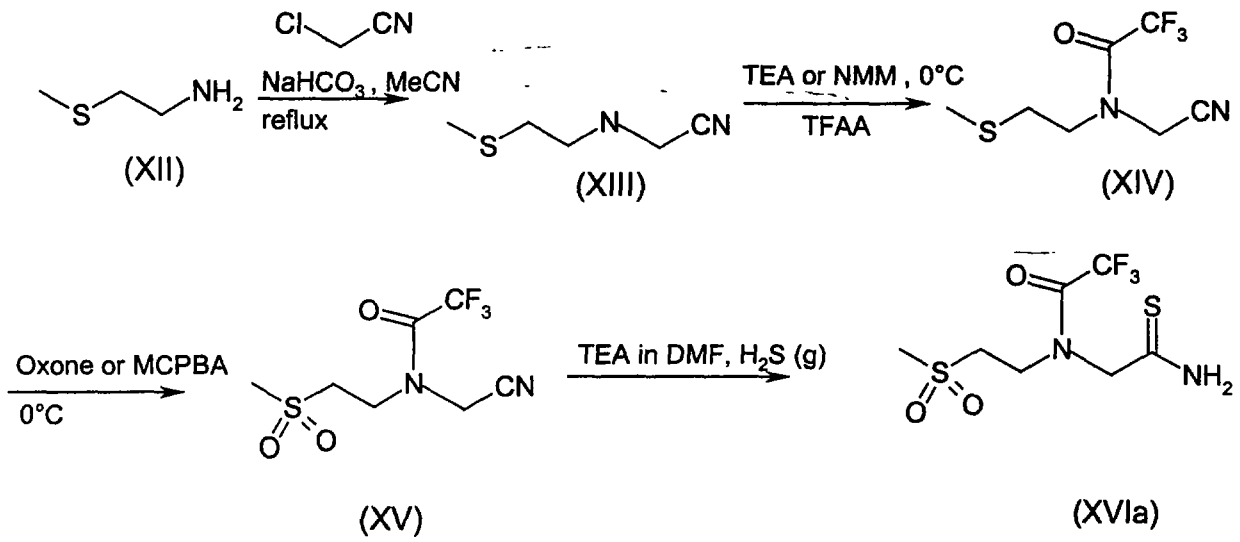
Scheme 1 outlines, for example, the synthesis of derivatives carrying a substituted thiazole ring as an R^1 substituent:



Scheme 1

wherein Hal' is a halogen atom (preferably iodo), and P' in the compound of formula (XI) is a suitable protecting group, such as trifluorocarbonyl.

An appropriately substituted thioamide coupling reagent, suitable for preparation of a thiazole ring system, may be prepared according to Scheme 2:



Scheme 2

Wherein in scheme 2 the trifluorocarbonyl protecting group in the compounds of formula (XIV), (XV) and (XVIa) is equivalent to the group P' in scheme 1.

Alternatively, an analogous scheme to those described above could be used wherein the substitution of the group R^1 onto the basic ring system occurs prior to the coupling reaction with the compound of formula(III).

Other substituted thioamides are prepared using analogous processes to that shown above.

In general, the group R^2 will be present as a substituent in the basic ring system prior to the introduction of the group R^1 or the anilino group. Where R^2 is other than hydrogen it may in certain circumstances be necessary to protect the group prior to performing the reaction steps to introduce the R^1 and anilino substituents. Particular mention should be made of the situation where R^2 is hydroxy; suitable protecting groups to ensure non-interference with the subsequent reaction steps include the 2-

methoxyethoxymethyl ether (MEM) group or a bulky silyl protecting group such as tert-butyldiphenylsilyl (TBDPS).

Suitable protecting groups, methods for their introduction and methods for their removal would be well known to the person skilled in the art. For a description of protecting groups and their use see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd edn., John Wiley & Sons, New York, 1991.

Suitable leaving groups for L and L' will be well known to those skilled in the art and include, for example, halo such as fluoro, chloro, bromo and iodo; sulphonyloxy groups such as methanesulphonyloxy and toluene-p-sulphonyloxy; alkoxy groups; and triflate.

The coupling reaction referred to above with the compound of formula (III) is conveniently carried out in the presence of a suitable inert solvent, for example a C_{1-4} alkanol, such as isopropanol, a halogenated hydrocarbon, an ether, an aromatic hydrocarbon or a dipolar aprotic solvent such as acetone, acetonitrile or DMSO at a non-extreme temperature, for example from 0 to 150°C, suitably 10 to 120°C, preferably 50 to 100°C.

Optionally, the reaction is carried out in the presence of a base. Examples of suitable bases include an organic amine such as triethylamine, or an alkaline earth metal carbonate, hydride or hydroxide, such as sodium or potassium carbonate, hydride or hydroxide.

The compound of formula (I) may be obtained from this process in the form of a salt with the acid HL, wherein L is as hereinbefore defined, or as the free base by treating the salt with a base as hereinbefore defined.

The compounds of formulae (II) and (III) as defined above, the reagents to substitute the group R^1, and the reagent(s) to convert the group T into the group R^1 are either readily available or can be readily synthesised by those skilled in the art using conventional methods of organic synthesis.

As indicated above, the compound of formula (I) prepared may be converted to another compound of formula (I) by chemical transformation of the appropriate substituent or substituents using appropriate chemical methods (see for example, J.March "Advanced Organic Chemistry", Edition III, Wiley Interscience, 1985).

Similar chemical transformations may also be used to convert any relevant intermediate compound to another intermediate compound prior to the final reaction to prepare a compound of formula (I); this would thus include their use to convert one compound of formula (III) to a further compound of formula (III) prior to any subsequent reaction.

The compounds of formula (I) and salts thereof have anticancer activity as demonstrated hereinafter by their inhibition of the protein tyrosine kinase c-erbB-2, c-erbB-4 and/or EGF-R enzymes and their effect on selected cell lines whose growth is dependent on c-erbB-2 or EGF-r tyrosine kinase activity.

The present invention thus also provides compounds of formula (I) and pharmaceutically acceptable salts or solvates thereof for use in medical therapy, and particularly in the treatment of disorders mediated by protein tyrosine kinase activity such as human malignancies and the other disorders mentioned above. The compounds of the present invention are especially useful for the treatment of disorders caused by aberrant c-erbB-2 and/or EGF-r activity such as breast, ovarian, gastric, pancreatic, non-small cell lung, bladder, head and neck cancers, and psoriasis.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from a disorder mediated by protein tyrosine kinase activity, including susceptible malignancies, which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in therapy.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of cancer and malignant tumours.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of psoriasis.

Whilst it is possible for the compounds, salts or solvates of the present invention to be administered as the new chemical, it is preferred to present them in the form of a pharmaceutical formulation.

According to a further feature of the present invention there is provided a pharmaceutical formulation comprising at least one compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain for example 0.5mg to 1g, preferably 70mg to 700mg, more preferably 5mg to 100mg of a compound of the formula (I) depending on the condition being treated, the route of administration and the age, weight and condition of the patient.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

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

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

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

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

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

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The animal requiring treatment with a compound, salt or solvate of the present invention is usually a mammal, such as a human being.

A therapeutically effective amount of a compound, salt or solvate of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian However, an effective amount of a compound of the present invention for the treatment of neoplastic

growth, for example colon or breast carcinoma, will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate of the present invention may be determined as a proportion of the effective amount of the compound per se. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

The compounds of the present invention and their salts and solvates may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in anti-cancer therapy, combination with other chemotherapeutic, hormonal or antibody agents is envisaged. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one other pharmaceutically active agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Certain embodiments of the present invention will now be illustrated by way of example only. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

^{1}H NMR spectra were obtained at 500MHz on a Bruker AMX500 spectrophotometer, on a Bruker spectrophotometer at 300MHz, on a Bruker AC250 or Bruker AM250 spectrophotometer at 250MHz and on a Varian Unity Plus NMR spectrophotometer at 300 or 400 MHz. J values are given in Hz. Mass spectra were obtained on one of the following machines: VG Micromass Platform (electrospray positive or negative), HP5989A Engine (thermospray positive) or Finnigan-MAT LCQ (ion trap) mass

spectrometer. Analytical thin layer chromatography (tlc) was used to verify the purity of some intermediates which could not be isolated or which were too unstable for full characterisation, and to follow the progess of reactions. Unless otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254). Unless otherwise stated, column chromatography for the purification of some compounds used Merck Silica gel 60 (Art. 1.09385, 230-400 mesh), and the stated solvent system under pressure.

Petrol refers to petroleum ether, either the fraction boiling at 40-60°C, or at 60-80°C.
Ether refers to diethylether.
DMSO refers to dimethylsulphoxide.
THF refers to tetrahydrofuran.
HPLC refers to high pressure liquid chromatography.
NMM refers to *N*-methylmorpholine

Useful preparative techniques are described in WO96/09294, WO97/03069, WO97/13771, WO95/19774, WO96/40142 and WO97/30034; also described in these publications are appropriate intermediate compounds other than those detailed below.

Preparation processes specified in the prior art or in the experimental details below for compounds with a particular basic ring system (1) to (6) above may be suitably adapted for others of these basic ring systems.

General Procedures

(A) Reaction of an amine with a bicyclic species containing a 4-chloropyrimidine or 4-chloropyridine ring

The optionally substituted bicyclic species and the specified amine were mixed in an appropriate solvent (typically acetonitrile unless otherwise specified, although ethanol, 2-propanol or DMSO may also be used), and heated to reflux. When the reaction was complete (as judged by tlc), the reaction mixture was allowed to cool. The resulting suspension was diluted, *e.g.* with acetone, and the solid collected by filtration, washing *e.g.* with excess acetone, and dried at 60°C *in vacuo*, giving the product as the hydrochloride salt. If the free base was required

(*e.g.* for further reaction), this was obtained by treatment with a base *e.g.* triethylamine; purification by chromatography was then performed if required.

(B) Reaction of a product from Procedure (A) with a heteroaryl tin reagent

A stirred mixture of the product from Procedure (A) (containing a suitable leaving group such as chloro, bromo, iodo or triflate), a heteroaryl stannane and a suitable palladium catalyst, such as bis(triphenylphosphine)palladium (II) chloride or 1,4-bis(diphenylphosphino)butane palladium (II) chloride (prepared as described in C.E. Housecroft et. al., Inorg. Chem., (1991), 30(1), 125-130), together with other appropriate additives (such as diisopropylethylamine or lithium chloride), were heated at reflux in dry dioxane or another suitable solvent (e.g. DMF) under nitrogen until the reaction was complete. The resulting mixture was generally purified by chromatography on silica.

(C) Removal of a 1,3-dioxolan-2-yl protecting group to liberate an aldehyde

The compound containing the 1,3-dioxolan-2-yl group was suspended in an appropriate solvent, e.g.THF and treated with hydrochloric acid, either as an aqueous solution (e.g. 2N) or as a solution in dioxane (e.g. 4 molar) and stirred at ambient temperature until the reaction was judged complete (e.g. by tlc or LC/MS analysis). Generally the mixture was diluted with water, and the resulting precipitate was collected by filtration, washed with water and dried to give the aldehyde.

(D) Reaction of an aldehyde with an amine by reductive amination

An aldehyde (such as the product of General Procedure C) and the required primary or secondary amine were stirred together in a suitable solvent (such as dichloromethane) containing glacial acetic acid (4A molecular sieves may also be present) for ca. 1h. A suitable reducing agent, such as sodium (triacetoxy) borohydride was then added and stirring continued under nitrogen until the reaction was complete (as judged by hplc or tlc). The resulting mixture was washed with an aqueous basic solution (e.g. sodium or potassium carbonate) and extracted with a suitable solvent, e.g. dichloromethane. The dried organic phase was evaporated and the residue purified either by column chromatography or by Bond Elut™ cartridge. If desired, the isolated material was

then converted into the hydrochloride salt e.g. by treatment with ethereal hydrogen chloride.

(E) Reaction sequence to prepare appropriately substituted thioamides

E-1 Reaction of an aminosulfide with chloroacetonitrile

To a stirred mixture of an aminosulfide and a suitable base such as sodium bicarbonate or sodium carbonate in an appropriate solvent (typically acetonitrile, although DMF or dioxane can be used) was added chloroacetonitrile dropwise. The resulting mixture was heated to reflux until the reaction was complete. The solid was filtered and the filtrate was concentrated to provide the corresponding aminonitrile.

E-2 Trifluoroacetamide protection of an aminonitrile

A solution of the aminonitrile (such as the product of general procedure A) and an amine base, such as triethylamine or NMM in a suitable solvent (e.g. dichloromethane), was cooled to 0°C and trifluoroacetic anhydride was added dropwise. The resulting mixture was stirred at room temperature until the reaction was complete. Water was added and the mixture was extracted with a suitable solvent (e.g. dichloromethane), the organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude product was purified by column chromatography to provide the corresponding trifluoroacetamide.

E-3 Oxidation of a cyanosulfide

To a stirred solution of a sulfide (such as the product of general procedure E1) in a suitable solvent (typically methanol/water (2:1), although dichloromethane can be used) cooled to 0°C was added an oxidizing agent (typically oxone, although MCPBA can be used). The resulting mixture was stirred at room temperature until the reaction was complete. The reaction was concentrated to remove any organic solvents, diluted with water, and extracted with an appropriate solvent (e.g. dichloromethane). The organic layer was dried and concentrated to provide the corresponding cyanosulfone.

E-4 Preparation of thioamides

To a solution of a cyanosulfone (such as the product of general procedure E-3) and an organic base (e.g. triethylamine) in THF was added hydrogen sulfide gas. The

resulting mixture was stirred at room temperature until the reaction was complete. The mixture was concentrated and triturated with hexane to provide thioamide.

(F) Reaction sequence to prepare an optionally substituted thiazole

F-1 Reaction of a vinylstannane with a product from Procedure (A)
A stirred mixture of the optionally substituted bicyclic 4-anilinopyrimidine species, tributyl(1-ethoxyvinyl)stannane (1 to 5 molar equivalents), and a suitable palladium catalyst (0.03 to 0.1 molar equivalents), such as bis(triphenylphosphine) palladium (II) chloride or tetrakis(triphenylphosphine) palladium (0) was heated at reflux in an appropriate solvent (typically acetonitrile, although DMF or dioxane can be used) until the reaction was complete. The resulting mixture was concentrated and generally purified by trituration with diethyl ether to provide the corresponding bicyclic pyrimidine vinyl ether.

F-2 Reaction of a product from Procedure (F-1) with a bromination reagent
A bicyclic pyrimidine vinyl ether (such as the product of general procedure F-1) and 1 equivalent of a bromination reagent, such as N-bromosuccinimide or bromine, were stirred at 0°C in a suitable solvent (typically 10% aqueous THF or dichloromethane) until the reaction was complete. The resulting mixture was dried over anhydrous magnesium sulfate and concentrated, or in the case of bromine the solid was filtered, to provide the corresponding α-bromoketone.

F-3 Reaction of a product from procedure (F-2) with a product from Procedure (E-4)
A stirred mixture of an α-bromoketone (such as the product of general procedure F-2) and thioamide from Procedure E-4 in a 1:1 molar ratio was heated to 70-100°C in an appropriate solvent (typically DMF, although acetonitrile and THF can be used) until the reaction was complete. The resulting mixture was washed with an aqueous basic solution (e.g. sodium carbonate) and extracted with a suitable solvent, e.g. ethyl acetate. The dried organic layer was concentrated and the residue was purified by column chromatography to provide the corresponding trifluoroacetamide aminothiazole.

F-4 Removal of a trifluoroacetamide protecting group to liberate an aminothiazole

A mixture of a trifluoroacetamide protected aminothiazole (such as the product of general procedure F-3) in 2M NaOH/methanol (1:1) was stirred at room temperature until the reaction was complete. The mixture was concentrated, poured into water and extracted with an appropriate solvent e.g. 10% MeOH/dichloromethane. The dried organic layer was concentrated, then dissolved in ethyl acetate/MeOH (1:1) and treated with 4M HCl/dioxane. The resulting solid was filtered to provide the corresponding amine hydrochloride salt.

Synthesis of Intermediates

N-5-[*N*-*tert*-Butoxycarbonyl)amino]-2-chloropyridine

A stirred solution of 6-chloronicotinic acid (47.3g), diphenylphosphoryl azide (89.6g) and triethylamine (46ml) in t-butanol (240ml) were heated under reflux under nitrogen for 2.5 hours. The solution was cooled and concentrated *in vacuo*. The syrupy residue was poured into 3 litres of a rapidly stirred solution of 0.33N aqueous sodium carbonate. The precipitate was stirred for one hour and filtered. The solid was washed with water and dried *in vacuo* at 70°C to give the title compound (62g) as a pale brown solid; m.p. 144-146°C; δH [$^2H_6$]-DMSO 8.25(1H,d), 7.95 (1H, bd), 7.25 (1H, d), 6.65(1H, bs), 1.51 (9H,s); m/z $(M + 1)^+$ 229.

This material may subsequently be carried forward to the appropriately substituted pyridopyrimidine intermediate according to the procedures as described in WO95/19774, J. Med. Chem., 1996, 39, pp 1823-1835, and J. Chem. Soc., Perkin Trans. 1, 1996, pp 2221-2226. Specific compounds made by such procedures include 6-chloro-pyrido[3,4-d]pyrimidin-4-one and 4,6-dichloro-pyrido[3,4-d]pyrimidine.

2-Amino-4-fluoro-5-iodo-benzoic acid

To a vigorously stirred solution of dichloromethane (700 ml), methanol (320 ml), and 2-amino-4-fluoro-benzoic acid (33.35 grams, 215 mmoles) was added solid sodium hydrogencarbonate (110 grams, 1.31 moles) followed by portion addition of benzyltrimethyl ammonium dichloroiodate (82.5 grams, 237 mmoles). The mixture was allowed to stir for 48 hours. The mixture was filtered to remove the insolubles. The remaining solid residue was washed with 200 ml of dichloromethane. The filtrate was concentrated and redissolved in a one to one

mixture of ethyl acetate (1 litre) and a 0.2 N solution of sodium hydroxide (1 litre), added to a 2 litre separatory funnel and extracted. The organic layer was washed with an additional 200 ml of water. The aqueous layers were combined and acidified with 2N hydrochloric acid. The resulting precipitate was collected by suction filtration, washed with water and dried under vacuum at 60°C to yield 46.5 grams (77%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.04(d, 1H), 7.1(s, broad, 2H), 6.63(d, 1H). ESI-MS m/z 280 (M-1).

4-Fluoro-5-iodo-isatoic anhydride

Anhydrous dioxane (0.5 litres), 2-amino-4-fluoro-5-iodo-benzoic acid (46 grams, 164 mmoles), and trichloromethylchloroformate (97.4 grams, 492 mmoles) were added to a one litre one neck flask equipped with a magnetic stir bar and reflux condenser. The solution was placed under anhydrous nitrogen, stirred and heated to reflux for 16 hours. The reaction mixture was allowed to cool and was poured into one litre of hexanes. The solid was collected by suction filtration, washed with an additional 0.5 litres of hexanes, and dried under vacuum at room temperature to yield 45.5 grams (90%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.86(s, 1H), 8.24(d, 1H), 6.84(d, 1H). ESI-MS m/z 308 (M+1).

4-Chloro-6-bromoquinazoline and 4-Chloro-6-iodoquinazoline were prepared as described in WO 96/09294.

4-Hydroxy-6-iodo-7-fluoroquinazoline

Dimethylformamide (0.5 litres), 4-fluoro-5-iodo-isatoic anhydride (45 grams, 147 mmoles), and formamidine acetate (45.92 grams, 441 mmoles), were combined in a one litre one-neck flask fitted with a magnetic stir bar. The mixture was placed under anhydrous nitrogen and heated at 110°C for 6 hours. The mixture was allowed to cool, followed by concentrating the reaction mixture to one third its original volume on the rotary evaporator. The resulting mixture was poured onto 3 litres of ice water. The resulting precipitated solid was collected by suction filtration. The solid was washed with an additional one litre of distilled water. The resulting solid was dried under vacuum at 70°C to yield 38.9 grams (91%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.43(s, 1H), 8.46(d, 1H), 8.12(s, 1H), 7.49(d, 1H). ESI-MS m/z 291(M+1).

4-Chloro-6-iodo-7-fluoro-quinazoline hydrochloride

Thionyl chloride (0.6 litres), 4-hydroxy-6-iodo-7-fluoro-quinazoline (36 grams, 124 mmoles), and dimethylformamide (6 ml) were combined in a one litre one-neck flask fitted with a magnetic stir bar. The mixture was placed under anhydrous nitrogen and heated to a gentle reflux for 24 hours. The mixture was allowed to cool, followed by concentrating the reaction mixture to a thick yellowish residue. To this residue was added dichloromethane (0.1 litre) and toluene (0.1 litre). The mixture was concentrated to dryness. This procedure was repeated two additional times. To the resulting solid was added 0.5 litres of dry dichloromethane and the mixture was stirred for one hour. The mixture was filtered and the remaining solids were washed with minimal dichloromethane. The dichoromethane filtrates were combined, concentrated to a solid, and dried under vacuum at room temperature to yield 28.6 grams (67%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ: 9.03(s, 1H), 8.76(d, 1H), 7.69(d, 1H). ESI-MS m/z 309(M+1).

2-Bromo-4-(1,3-dioxolan-2-yl) thiazole

2-Bromothiazole-4-carbaldehyde (6.56g,34.17mmol) [A.T. Ung, S.G.Pyne/ Tetrahedron: Asymmetry 9 (1998) 1395-1407]and ethylene glycol (5.72ml, 102.5 mmol) were heated under reflux in toluene (50ml) ,with a Dean and Stark trap fitted, for 18hr. The product was concentrated and purified by column chromatography (15% ethyl acetate /hexane) to give the product as a yellow solid (6.03g); m/z 236,238.

4-(1,3-Dioxolan-2-yl)-5-(tributylstannyl)thiazole

2-Bromo-4-(1,3-dioxolan-2-yl) thiazole (6.4 g ,27.14 mmol) was stirred at –78° C in dry THF (38ml).1.6M n butyl lithium in hexane (18.6ml, 29.78 mmol) was added dropwise under nitrogen. After 30min at this temperature, tributyl tin chloride (7.35ml,27.14 mmol) was added dropwise. The reaction was allowed to warm to 0° and water (20ml) was added. The product was extracted into ether (3x100ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was triturated with isohexane (3x100ml) and the mother liquors were decanted, combined and concentrated to give a brown oil (11.88g); m/z 444 – 450.

Substituted anilines were in general prepared by analogous methods to those outlined in WO 96/09294 and/or as follows:

Step 1: Preparation of the precursor nitro-compounds

4-Nitrophenol (or an appropriate substituted analogue, such as 3-chloro-4-nitrophenol) was treated with a base such as potassium carbonate or sodium hydroxide in an appropriate solvent, such as acetone or acetonitrile. The appropriate aryl or heteroaryl halide was added and the reaction mixture heated or stirred at room temperature overnight.

Purification A: Most of the acetonitrile was removed *in vacuo*, and the residue was partitioned between water and dichloromethane. The aqueous layer was extracted with further dichloromethane (x 2), and the combined dichloromethane layers were concentrated *in vacuo*.

Purification B: removal of insoluble material by filtration, followed by concentration of the reaction mixture *in vacuo,* and chromatography on silica.

Step 2: Reduction to the corresponding aniline

The precursor nitro compound was reduced by catalytic hydrogenation at atmospheric pressure using 5% Pt/carbon, in a suitable solvent (eg ethanol, THF, or mixtures thereof to promote solubility). When reduction was complete, the mixture was filtered through Harborlite™, washing with excess solvent, and the resulting solution concentrated *in vacuo* to give the desired aniline. In some cases, the anilines were acidified with HCl (e.g. in a solution in dioxane) to give the corresponding hydrochloride salt.

Anilines prepared by such methods include:
4-(3-Fluorobenzyloxy)aniline; m/z $(M+1)^+$ 218
3-Chloro-4-(2-fluorobenzyloxy)aniline; m/z $(M+1)^+$ 252
3-Chloro-4-(3-fluorobenzyloxy)aniline; m/z $(M+1)^+$ 252
3-Chloro-4-(4-fluorobenzyloxy)aniline; m/z $(M+1)^+$ 252
4-Benzyloxy-3-chloroaniline; m/z $(M+1)^+$ 234
and, in appropriate cases, their hydrochloride salts.

4-(Tributylstannyl)thiazole-2-carbaldehyde

4-Bromo-2-(tributylstannyl)thiazole (T.R. Kelly and F. Lang, *Tetrahedron Lett.*, 36, 9293, (1995)) (15.0g) was dissolved in THF (150ml) under a nitrogen atmosphere, cooled to –85°C and treated with *t*-BuLi (1.7M, in pentane, 43ml). The mixture was stirred at –85°C for 30min, and then *N*-formylmorpholine (8.4g) was added by syringe. After further stirring at –85°C for 10min the mixture was allowed to warm to room temperature. Water (200ml) was added and the mixture was extracted with diethyl ether (4 x 100ml). The combined ethereal extracts were washed with water, dried ($NaSO_4$), and concentrated *in vacuo.* Chromatography on silica, eluting with 10%ether/*i*-hexane, gave the title compound as a yellow oil; δH [$^2H_6$]DMSO 10.03 (1H,s), 8.29 (1H,s), 1.55(6H,q), 1.21-1.37 (6H,m), 1.09-1.20 (6H,m), 0.85 (9H,t).

6-Iodo-(4-(3-fluorobenzyloxy)-3-chlorophenyl)-quinazolin-4yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-3-chlorophenyl)amine and 4-chloro-6-iodo-quinazoline. ^1H NMR (DMSO-d6) 9.83 (s, 1H); 8.92 (s, 1H); 8.58 (s, 1H); 8.09 (d, 1H); 8.00 (d, 1H); 7.61 (d, 1H); 7.52 (d, 1H); 7.44 (m, 1H); 7.20-7.33 (m, 3H); 7.15 (m, 1H); 5.21 (s, 2H); MS *m/z* 506 (M+1).

6-Iodo-(4-(3-fluorobenzyloxy)-3-fluorophenyl)-quinazolin-4yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-3-fluorophenyl)amine and 4-chloro-6-iodo-quinazoline. ^1H NMR (DMSO-d6) 9.83 (s, 1H); 8.92 (s, 1H); 8.57 (s, 1H); 8.08 (d, 1H); 7.85 (d, 1H); 7.53 (d, 1H); 7.50 (d, 1H); 7.43 (m, 1H); 7.30-7.20 (m, 3H); 7.15 (m, 1H); 5.20 (s, 2H); MS *m/z* 490 (M+1).

6-Iodo-(4-(3-fluorobenzyloxy)-3-methoxyphenyl)-quinazolin-4yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-3-methoxyphenyl)amine and 4-chloro-6-iodo-quinazoline. ^1H NMR 400 MHz (DMSO-d6) 11.29 (bs, 1H0; 9.14 (s,1H); 8.87 (s,1H); 8.32 (d,1H); 7.62 (d,1H); 7.42 (m,1H); 7.34 (d,1H); 7.29-7.22 (m,3H); 7.18-7.08 (m,2H); 5.15 (s,2H); 3.80 (s,3H); MS *m/z* 502 (M+1)

6-Iodo-(4-benzyloxy-3-fluorophenyl)-quinazolin-4-yl)amine

Prepared according to Procedure A from 4-benzyloxy)-3-fluorophenylamine and 4-chloro-6-iodo-quinazoline. ^1H NMR (DMSO-d6) 9.82 (s, 1H); 8.93 (s, 1H); 8.57 (s,

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1H); 8.09 (d, 1H); 7.84 (d, 1H); 7.51 (m, 2H); 7.44 (d, 2H); 7.37 (m, 2H); 7.33 (m, 1H); 7.24 (m, 1H); 5.18 (s, 2H); MS *m/z* 472 (M+1)

6-Iodo-(4-(3-fluorobenzyloxy)-phenyl)-quinazolin-4-yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-phenyl)amine and 4-chloro-6-iodo-quinazoline. ^{1}H NMR (DMSO-d6) 9.77 (s, 1H); 8.92 (s, 1H); 8.50 (s, 1H); 8.06 (d, 1H); 7.66 (d, 2H); 7.50 (d, 1H); 7.42 (m, 1H); 7.30-7.25 (m, 2H); 7.14 (m, 1H); 7.03 (d, 2H); 5.13 (s, 2H); MS *m/z* 472 (M+1)

6-(5-(1,3-Dioxolan-2-yl)-furan-2-yl)-7-methoxy-quinazolin-4-yl-(4-benzenesulphonyl)phenyl-amine

Prepared according to Procedure B from 4-(4-benzenesulphonyl)phenyl-7-methoxy-quinazolin-4-yl-amine and 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan. δ^1H NMR (400 MHz, DMSO-d_6) 10.36(s, 1H), 8.74(s, 1H), 8.58(s, 1H), 8.10(d, 2H), 7.93(m, 4H), 7.62(m, 3H), 7.32(s, 1H), 7.04(d, 1H), 6.68(d, 1H), 5.99(s, 1H), 4.09(m, 2H), 4.04(s, 3H), 3.95(m, 2H). ESI-MS m/z 530(M+1).

(6-Chloropyrido[3,4-d]pyrimidin-4-yl)-(4-(3-fluorobenzyloxy)-phenyl)-amine

4,6-Dichloro-pyrido[3,4-d]pyrimidine (1g) and 4-(3-fluorobenzyloxy)aniline (1.08g) in acetonitrile (70ml) were reacted together as in Procedure A. The product was collected by filtration as a yellow solid (1.86g); m/z 381 $(M+1)^+$.

(6-(5-(1,3-Dioxolan-2-yl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-(4-(3-fluorobenzyloxy)-phenyl)-amine

(6-Chloropyrido[3,4-d]pyrimidin-4-yl)-(4-(3-fluorobenzyloxy)-phenyl)-amine (1.85g) and 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)-furan (3.82g) in dioxan (40ml) were reacted together as in Procedure B. The mixture was evaporated and the residue suspended in dichloromethane. This was then filtered through Celite® and the solvent evaporated. The gummy residue was then triturated with hexane giving a beige solid (1.74g); m/z 485 $(M+1)^+$.

5-(4-(4-(3-Fluorobenzyloxy)-phenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-3-carbaldehyde

(6-Chloropyrido[3,4-d]pyrimidin-4-yl)-(4-(3-fluorobenzyloxy)-phenyl)-amine (1g) and 5-(tributylstannyl)-furan-3-carbaldehyde (J.Org.Chem. (1992), 57(11), 3126-31)

(1.84g) in dioxan (35ml) were reacted together as in Procedure B. The solvent was evaporated and the residue suspended in dichloromethane. The mixture was filtered through Celite® and then evaporated. The residue was triturated with hexane giving a beige solid (1g); m/z 441 $(M+1)^+$.

5-(4-(4-(3-Fluorobenzyloxy)-phenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde

(6-(5-(1,3-Dioxolan-2-yl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-(4-(3-fluorobenzyloxy)-phenyl)-amine (500mg) was treated with acid as in Procedure C. The product was collected by filtration as a beige solid (251mg); m/z 441 $(M+1)^+$.

(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-(2-(methylthio)-ethylaminomethyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine

(5-(4-(4-(3-Fluorobenzyloxy)-phenyl)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde (125mg) and (methylthio)ethylamine (0.08ml) in dichloromethane (5ml) were reacted together as in Procedure D. Purification using a Bond Elut™ cartridge gave a yellow oil (80mg); m/z 516 $(M+1)^+$.

Other suitable intermediates prepared by analogous methods to those described above are:

(4-Benzyloxy-3-chlorophenyl)-6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-3-bromophenyl)-6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-(3-Fluoro-benzyloxy)-3-bromophenyl)-6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-3-fluorophenyl)-6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-(3-Fluoro-benzyloxy)-3-fluorophenyl)-6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;

5-((4-Benzyloxy-3-chlorophenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;

5-((4-(3-Fluoro-benzyloxy)-3-chlorophenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;

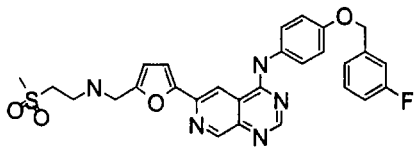
5-((4-Benzyloxy-3-bromophenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;

5-((4-(3-Fluoro-benzyloxy-3-bromophenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;

5-((4-Benzyloxy-3-fluorophenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carboxaldehyde;
5-((4-(3-Fluoro-benzyloxy-3-fluorophenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;
N-[4-(Benzyloxy)-3-chlorophenyl]-7-fluoro-6-chloro-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-fluoro-6-chloro-4-quinazolinamine;
N-[4-Benzyloxy-3-bromophenyl]-7-fluoro-6-chloro-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-bromophenyl]-7-fluoro-6-chloro-4-quinazolinamine;
N-[4-Benzyloxy-3-fluorophenyl]-7-fluoro-6-chloro-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy-3-fluorophenyl]-7-fluoro-6-chloro-4-quinazolinamine;
5-(4-[4-(Benzyloxy)-3-chlorophenylamino]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;
5-(4-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;
5-(4-[4-Benzyloxy-3-bromophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;
5-(4-[4-(3-Fluoro-benzyloxy)-3-bromophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;
5-[4-Benzyloxy-3-fluorophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde
5-(4-(3-Fluoro-benzyloxy)-3-fluorophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde.

Examples

Example 1

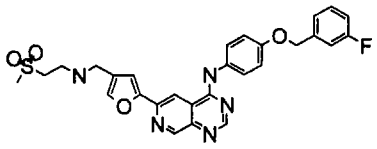


(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine dihydrochloride

(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-(2-(methylthio)-ethylaminomethyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine (80mg) in methanol (9ml) and water (3ml) was treated with Oxone™ (153mg) at room temperature for 2 days. The mixture was then partitioned between aqueous sodium carbonate solution and dichloromethane.

The dried organic phase was evaporated and the residue purified by Bond Elut™ cartridge, followed by conversion to the hydrochloride salt, giving a yellow solid (69mg); δH [$^2H_6$]DMSO 9.8 (1H,bs) 9.4 (1H,s) 9.3 (1H,s) 8.7 (1H,s) 7.8 (2H,d) 7.3-7.4 (2H,m) 7.0-7.3 (5H,m) 6.8 (1H,d) 5.3 (2H,s) 4.4 (2H,s) 3.5-3.7 (4H,m) 3.1 (3H,s); m/z 548 $(M+1)^+$.

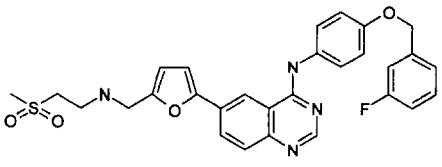
Example 2



(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine dihydrochloride

5-(4-(4-(3-Fluorobenzyloxy)-phenyl)-pyrido[3,4-d]pyrimidin-6-yl)-furan-3-carbaldehyde (300mg) and 2-methanesulphonyl-ethylamine (335mg) in dichloromethane (15ml) were reacted together as in Procedure D. Purification using a Bond Elut™ cartridge, followed by conversion to the hydrochloride salt, gave a yellow solid (110mg); δH [$^2H_6$]DMSO 9.8 (2H,br) 9.3 (1H,s) 9.0 (1H,s) 8.8 (1H,s) 8.2 (1H,s) 8.0 (1H,s) 7.1-7.8 (7H,m) 7.0 (1H,s) 5.2 (2H,s) 4.1-4.3 (4H,brm) 3.3-3.5 (2H,bs) (hidden under H_2O peak) 3.2 (3H,s); m/z 548$(M+1)^+$.

Example 3

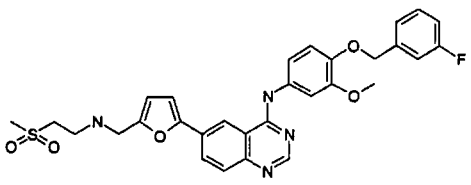


N-{4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{4-(3-fluorobenzyloxy)anilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^1H NMR 400 MHz (DMSO-d6) 9.40 (s,1H); 8.67 (s,1H); 8.30 (d,1H); 7.86 (d,1H); 7.75 (d,2H); 7.43 (m,1H); 7.30-7.21 (m,3H); 7.15 (m,1H); 7.07 (d,2H); 6.80

(d,1H); 5.15 (s,2H); 4.40 (s,2H); 3.65 (m,2H); 3.40 (m,2H); 3.11 (s,3H); MS *m/z* 547 (M+1).

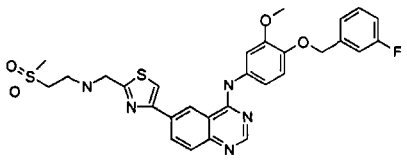
Example 4



N-{4-[(3-fluorobenzyl)oxy]-3-methoxyphenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-methoxy-4-(3-fluorobenzyloxy)anilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 9.22 (s,1H); 8.78 (s,1H); 8.31 (d,1H); 7.88 (d,1H); 7.50-7.08 (m,8H); 6.84 (d,1H); 5.13 (s,2H); 4.42 (s,2H); 3.80 (s,3H); 3.60 (m,2H); 3.40 (m, 2H, obscured by water peak); 3.10 (s,3H); MS *m/z* 577 (M+1).

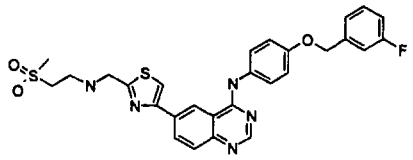
Example 5



N-{4-[(3-fluorobenzyl)oxy]-3-methoxyphenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-(4-(3-fluorobenzyloxy)-3-methoxypheny)quinazolin-4-ylamine (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv).^{1}H NMR 400 MHz (CD_3OD) 9.40 (s, 1H); 8.79 (s, 1H); 8.76 (d, 1H); 8.38 (s, 1H); 7.89 (d, 1H); 7.50 (s, 1H); 7.40 (t, 1H); 7.34 (m, 1H); 7.27 (d, 1H); 7.22 (d, 1H); 7.08 (d, 1H); 7.03 (t, 1H); 5.19 (s, 2H); 4.81 (s, 2H); 3.85 (m, 2H); 3.75 (m, 2H); 3.10 (s, 3H); MS m/z 594 $(M+1)^+$, 592 $(m-1)^-$.

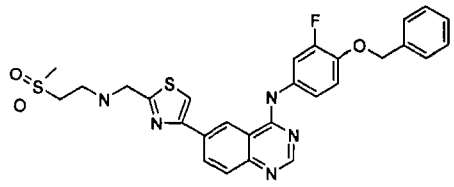
Example 6



N-{4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-(4-(3-fluorobenzyloxy)- phenyl)-quinazolin-4-ylamine and (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). ^{1}H NMR 400 MHz (CD_3OD) 9.44 (s, 1H); 8.79 (s, 1H); 8.76 (d, 1H); 8.37 (s, 1H); 7.90 (d, 1H); 7.74 (d, 1H); 7.53 (d, 1H); 7.46 (d, 2H); 7.38 (m, 2H); 7.32 (d, 1H); 7.24 (d, 1H); 5.21 (s, 2H); 4.82 (s, 2H); 3.85 (m, 2H); 3.77 (m, 2H); 3.11 (s, 3H); MS *m/z* 564 $(M+1)^+$, 562 $(m-1)^-$.

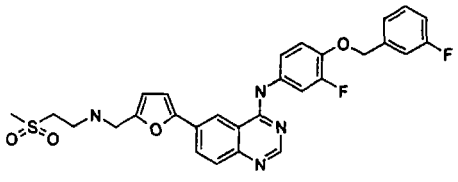
Example 7



N-[4-(benzyloxy)-3-fluorophenyl]-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-(4-benzyloxy)-3-fluorophenyl)quinazolin-4-ylamine and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). ^{1}H NMR 400 MHz (CD_3OD) 9.41 (s, 1H); 8.77 (d, 1H); 8.75 (s, 1H); 8.36 (s, 1H); 7.90 (d, 1H); 7.71 (d, 2H); 7.60 (m, 1H); 7.40 (m, 1H); 7.23 (m, 1H); 7.11 (d, 2H); 7.03 (m, 1H); 5.17 (s, 2H); 4.81 (s, 2H); 3.85 (m, 2H); 3.76 (m, 2H); 3.10 (s, 3H); MS m/z 564 $(M+1)^+$, 562 $(m-1)^-$.

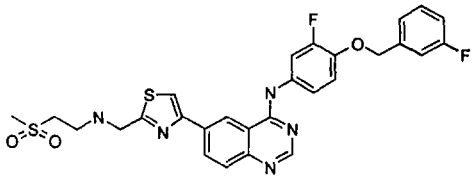
Example 8



N-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-fluoro-4-(3-fluorobenzyloxy)anilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 9.61 (bs, 2H); 9.28 (bs, 1H); 8.80 (s, 1H); 8.34 (d, 1H); 7.87 (m, 2H); 7.59 (d, 1H); 7.44 (m, 1H); 7.2 - 7.38 (m, 4H); 7.18 (m, 1H); 6.83 (s, 1H); 5.25 (s, 2H); 4.42 (s, 2H); 3.60 (m, 2H); 3.45 (m, 2H, obscured by water peak); 3.16 (s, 3H); MS *m/z* 565 (M+1).

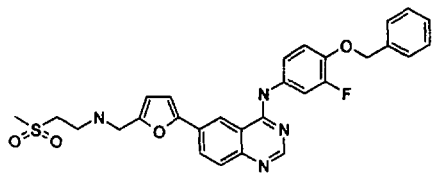
Example 9



N-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-4-(1-benzyl-1H-indazol-5-yl)-quinazolin-4-ylamine (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). ^{1}H NMR 400 MHz (CD_3OD) 9.28 (s, 1H); 8.78 (s, 1H); 8.74 (d, 1H); 8.31 (s, 1H); 7.90 (d, 1H); 7.74 (d, 1H); 7.63 (m, 1H); 7.54 (m, 1H); 7.49 (m, 1H); 7.37 (m, 1H); 7.25 (m, 2H); 7.05 (m, 1H); 5.24 (s, 2H); 4.77 (s, 2H); 3.81 (m, 2H); 3.72 (m, 2H); 3.10 (s, 3H); MS *m/z* 582 $(M+1)^+$, 580 $(m-1)^-$

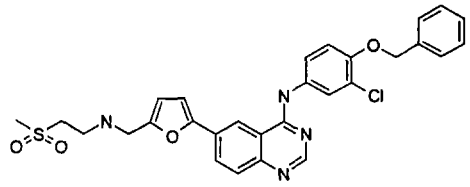
Example 10



N-(3-Fluoro-4-benzyloxyphenyl)-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-fluoro-4-benzyloxyanilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 8.83 (s,1H); 8.35 (d,1H); 7.89 (d,1H); 7.83 (d,1H); 7.59 (d,1H); 7.48-7.31 (m,7H); 7.26 (s,1H); 6.83 (d,1H); 5.21 (s,2H); 4.42 (s,2H); 3.60 (m,2H); 3.44 (m, 2H, obscured by water peak); 3.12 (s,3H); MS *m/z* 547 ($M+H^+$).

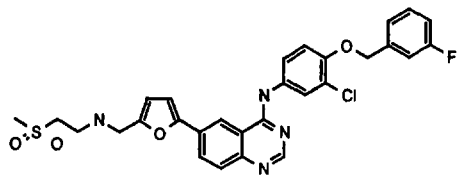
Example 11



N-(3-Chloro-4-benzyloxyphenyl)-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-chloro-4-benzyloxyanilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 9.71 (bs, 2H); 9.45 (bs, 1H); 8.86 (s, 1H); 8.36 (d, 1H); 7.98 (d, 1H); 7.90 (d, 1H); 7.74 (d, 1H); 7.49-7.44 (m, 2H); 7.40 (m, 2H); 7.35-7.30 (m, 2H); 7.28 (d, 1H); 6.83 (d, 1H); 5.25 (s, 2H); 4.42 (s, 2H); 3.62 (m, 2H); 3.44 (m, 2H); 3.12 (s, 3H); MS *m/z* 563 ($M+H^+$).

Example 12



N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-chloro-4-(3-fluorobenzyloxy)-anilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 9.60 (bs, 1H); 9.32 (bs, 1H); 8.82 (bs, 1H); 8.34 (d, 1H); 8.0 (s, 1H); 7.88 (d, 1H); 7.74 (d, 1H); 7.45 (m, 1H); 7.34-7.23 (m, 4H); 7.17 (m, 1H); 6.83 (d, 1H); 5.27 (s, 2H); 4.42 (s, 2H); 3.59 (m, 2H); 3.40 (m, 2H, obscured by waterpeak); 3.12 (s, 3H); MS *m/z* 581 ($M+H^+$).

Further Examples

The compounds in Lists 1 to 9 above and their hydrochloride salts, if appropriate, are prepared by analogous techniques using the appropriate starting materials.

Biological Data

Compounds of the present invention were tested for protein tyrosine kinase inhibitory activity in substrate phosphorylation assays and cell proliferation assays.

Substrate Phosphorylation Assay

The substrate phosphorylation assays use baculovirus expressed, recombinant constructs of the intracellular domains of c-erbB-2 and c-erbB-4 that are constitutively active and EGFr isolated from solubilised A431 cell membranes. The method measures the ability of the isolated enzymes to catalyse the transfer of the g-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide (Biotin-GluGluGluGluTyrPheGluLeuVal). Substrate phosphorylation was detected following either of the following two procedures: a.) c-ErbB-2, c-ErbB4 or EGFr were incubated for 30 minutes, at room temperature, with 10mM $MnCl_2$, 10mM ATP, 5 mM peptide, and test compound (diluted from a 5mM stock in DMSO, final DMSO concentration is 2%) in 40mM HEPES buffer, pH 7.4. The reaction was stopped by the addition of EDTA (final concentration 0.15mM) and a sample was transferred to

a streptavidin-coated 96-well plate. The plate was washed and the level of phosphotyrosine on the peptide was determined using a Europium-labelled antiphosphotyrosine antibody and quantified with a time-resolved fluorescence technique. b.) ErbB2 was incubated for 50 minutes at room temperature with 15 mM MnCl2, 2 mM ATP, 0.25 mCi [γ-^{33}P] ATP/well, 5 mM peptide substrate, and test compound (diluted from a 10mM stock in DMSO, final DMSO concentration is 2%) in 50 mM MOPS pH 7.2. The reaction was terminated by the addition of 200 ml of PBS containing 2.5 mg/ml streptavidin-coated SPA beads (Amersham Inc.), 50 mM ATP, 10 mM EDTA and 0.1%TX-100. The microtitre plates were sealed and SPA beads were allowed to settle for at least six hours. The SPA signal was measured using a Packard Topcount 96-well plate scintillation counter (Packard Instrument Co., Meriden, CT).

The results are shown in Tables 1A (examples 1 and 2) and 1B (examples 3 to 12) as the IC_{50} values.

Table 1A

	Substrate Phosphorylation	
Example	erbB2 – assay (b)	EGF-r – assay (a)
1	+++	+++
2	++	-

Table 1B

	Substrate Phosphorylation
Example	erbB2 – assay (b)
3	+++
4	+++
5	++
6	+++
7	+++
8	+++
9	+++
10	+++
11	+++
12	+++

IC_{50} values	Symbol
< 0.10 μM	+++
0.10 – 1.0 μM	++
1.0 – 10.0 μM	+
> 10.0 μM	-
Not determined	ND

Cellular assays: Methylene Blue Growth Inhibition Assay

Human breast (BT474), head and neck (HN5) and gastric tumor (N87) cell lines were cultured in low glucose DMEM (Life Technologies 12320-032) containing 10% fetal bovine serum (FBS) at 37°C in a humidified 10% CO_2, 90% air incubator. The SV40 transformed human mammary epithelial cell line HB4a was transfected with either human H-ras cDNA (HB4a r4.2) or the human c-erbB2 cDNA (HB4a c5.2). The HB4a clones were cultured in RPMI containing 10% FBS, insulin (5 μg/ml), hydrocortisone (5 μg/ml), supplemented with the selection agent hygromycin B (50μg/ml). Cells were harvested using trypsin/EDTA, counted using a haemocytometer, and plated in 100 ml of the appropriate media, at the following densities, in a 96-well tissue culture plate (Falcon 3075): BT474 10,000 cells/well, HN5 3,000 cells/well, N87 10,000 cells/well, HB4a c5.2 3,000 cells/well, HB4a r4.2 3,000 cells/well. The next day, compounds were diluted in DMEM containing 100 mg/ml gentamicin, at twice the final required concentration, from 10mM stock solutions in DMSO. 100ml/well of these dilutions were added to the 100ml of media currently on the cell plates. Medium containing 0.6% DMSO was added to control wells. Compounds diluted in DMEM were added to all cell lines, including the HB4a r4.2 and HB4a c5.2 cell lines. The final concentration of DMSO in all wells was 0.3%. Cells were incubated at 37°C, 10% CO_2 for 3 days. Medium was removed by aspiration. Cell biomass was estimated by staining cells with 100μl per well methylene blue (Sigma M9140, 0.5% in 50:50 ethanol:water), and incubation at room temperature for at least 30 minutes. Stain was removed, and the plates rinsed under a gentle stream of water, and air-dried. To release stain from the cells 100μl of solubilization solution was added (1% N-lauroyl sarcosine, Sodium salt, Sigma L5125, in PBS), and plates were shaken gently for about 30 minutes. Optical density at 620 nM was measured on a microplate reader. Percent inhibition of cell growth was calculated relative to vehicle treated control wells. Concentration of compound that inhibits 50% of cell growth (IC_{50}) was interpolated using nonlinear

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regression (Levenberg-Marquardt) and the equation, $y = V_{max}*(1-(x/(K+x))) + Y2$, where "K" was equal to the IC_{50}.

Table 2 illustrates the inhibitory activity of compounds of the present invention as IC_{50} values in μM against a range of tumor cell lines.

Table 2

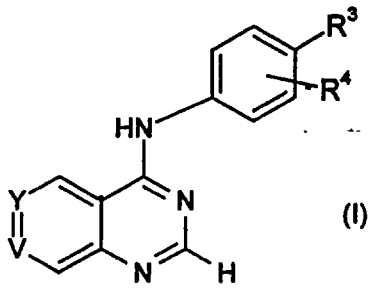
Example	Cell Proliferation				
	HB4a erbB2	HB4a ras	BT474	HN5	N87
1	+++	+	+++	+++	+++
2	+++	+	+++	+++	+++
3	+++	++	+++	+++	+++
4	+++	++	+++	+++	+++
5	+++	-	+++	++	+++
6	+++	-	+++	+++	+++
7	+++	-	+++	+++	+++
8	+++	++	+++	+++	+++
9	+++	-	+++	+++	+++
10	+++	++	+++	+++	+++
11	+++	+	+++	+++	+++
12	+++	-	+++	+++	+++

IC_{50} value	Symbol
< 5 μM	+++
5 – 25 μM	++
25 – 50 μM	+
> 50 μM	-
Not determined	**ND**

Claims

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1. A compound of formula (I)



(I)

or a salt or solvate thereof;

wherein
Y is CR^1 and V is N;
or Y is CR^1 and V is CR^2;

R^1 represents a group $CH_3SO_2CH_2CH_2NHCH_2$-Ar-, wherein Ar is selected from furan and thiazole, each of which may optionally be substituted by one or two halo, C_{1-4} alkyl or C_{1-4} alkoxy groups;

R^2 is hydrogen or C_{1-4} alkoxy; or R^2 is halo;

R^3 is selected from a group comprising benzyl, halo-, dihalo- and trihalobenzyl, benzoyl, pyridylmethyl, pyridylmethoxy, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl;

R^4 is halo or C_{1-4} alkoxy or is not present;

wherein
either (a) R^3 represents 3-fluorobenzyloxy;
and/or (b) R^4 is selected from halo and is substituted in the 3-position of the phenyl ring;

and halo represents fluoro, chloro or bromo.

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2. A compound as claimed in claim 1 wherein R^2 is hydrogen or methoxy; or R^2 is fluoro.

3. A compound as claimed in claim 1 or claim 2 wherein the group Ar represents unsubstituted furan or thiazole.

4. A compound as claimed in any one of claims 1 to 3 wherein R^3 represents benzyl, pyridylmethyl, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl.

5. A compound as claimed in any one of claims 1 to 4 wherein the R^4 group is not present.

6. A compound as claimed in any one of claims 1 to 5 wherein the phenyl group together with the substituent(s) R^3 and R^4 represents (3-fluorobenzyloxy)phenyl.

7. A compound as claimed in any one of claims 1 to 4 wherein the phenyl group together with the substituent(s) R^3 and R^4 represents 3-fluorobenzyloxy-3-chlorophenyl, benzyloxy-3-chlorophenyl, benzyloxy-3-fluorophenyl, or 3-fluorobenzyloxy-3-fluorophenyl.

8. A compound as claimed in claim 1 selected from:
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
N-{4-[(3-Fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-{4-[(3-Fluorobenzyl)oxy]-3-methoxyphenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-{4-[(3-Fluorobenzyl)oxy]-3-methoxyphenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

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N-{4-[(3-Fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

9. A compound as claimed in claim 1 selected from:
N-[4-(Benzyloxy)-3-fluorophenyl]-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-(3-Fluoro-4-benzyloxyphenyl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine;
N-(3-Chloro-4-benzyloxyphenyl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

10. A compound as claimed in claim 1 selected from:

(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;

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(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-bromophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-fluorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-fluorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-bromophenyl)-(6-(5-((2methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-bromophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-fluorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine
N-[4-(3-Fluoro-benzyloxy)-3-bromophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine
N-[4-(3-Fluoro-benzyloxy)-3-fluorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine
N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

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N-[4-(3-Fluoro-benzyloxy)-3-bromophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-fluorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-bromophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy)-3-fluorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

11. A compound as claimed in claim 1 selected from:

(4-Benzyloxy-3-chlorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-bromophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-fluorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-fluorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine
(4-Benzyloxy-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-3-bromophenyl)-(6-(5-((2methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
N-[4-(Benzyloxy)-3-chlorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-Benzyloxy-3-bromophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-Benzyloxy-3-fluorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

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N-[4-(Benzyloxy)-3-chlorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-Benzyloxy-3-bromophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine
N-[4-Benzyloxy-3-fluorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine
N-[4-(Benzyloxy)-3-chlorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-bromophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-fluorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(Benzyloxy)-3-chlorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-bromophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-fluorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

12. A compound as claimed in claim 8 selected from:
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

13. A compound as claimed in claim 10 selected from:
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

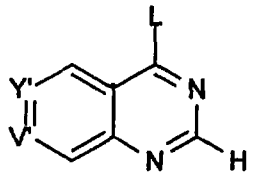
14. A compound as claimed in claim 10 selected from:
N-{3-Bromo-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

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and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

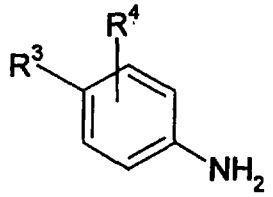
15. A compound as claimed in any one of claims 1 to 14 which inhibits both c-erbB-2 and EGF-R receptor kinases.

16. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises the steps:
(a) the reaction of a compound of formula (II)



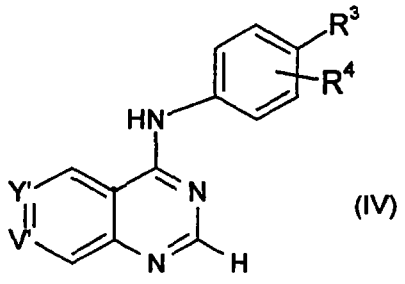
(II)

wherein Y' is CL' and V' is N;
or Y' is CL' and V' is CR^2;
wherein R^2 is as defined in claim 1, and L and L' are suitable leaving groups, with a compound of formula (III)



(III)

wherein R^3 and R^4 are as defined in claim 1, to prepare a compound of formula (IV)

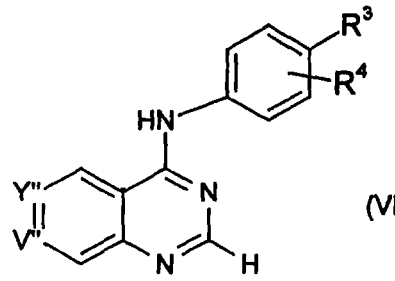


(IV)

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and subsequently (b) reaction with appropriate reagent(s) to substitute the group R^1 by replacement of the leaving group L'; and, if desired, (c) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

17. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises the steps:
(a) reacting a compound of formula (IV) as defined in claim 16 with appropriate reagent(s) to prepare a compound of formula (VIII)



(VIII)

wherein R^3 and R^4 are as defined in claim 1;
Y" is CT and V" is N;
or Y" is CT and V" is CR^2;
wherein R^2 is as defined in claim 1 and T is an appropriately functionalised group;
and (b) subsequently converting the group T into the group R^1 by means of appropriate reagent(s); and, if desired, (c) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

18. A pharmaceutical formulation comprising at least one compound of formula (I) as claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

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19. A pharmaceutical formulation as claimed in claim 18 in unit dosage form and containing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in an amount of from 70 to 700mg.

20. A compound of formula (I) as claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

21. The use of a compound of formula (I) as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for the treatment of a disorder mediated by c-erbB-2 and/or EGF-R protein tyrosine kinase activity.

22. The use as claimed in claim 21 wherein the compound is as claimed in claim 15.

23. The use as claimed in claim 22 wherein the compound is as claimed in any one of claims 12 to 14.

24. The use as claimed in any one of claims 21 to 23 in the preparation of a medicament for the treatment of cancer and malignant tumours.

25. The use as claimed in any one of claims 21 to 23 in the preparation of a medicament for the treatment of psoriasis.