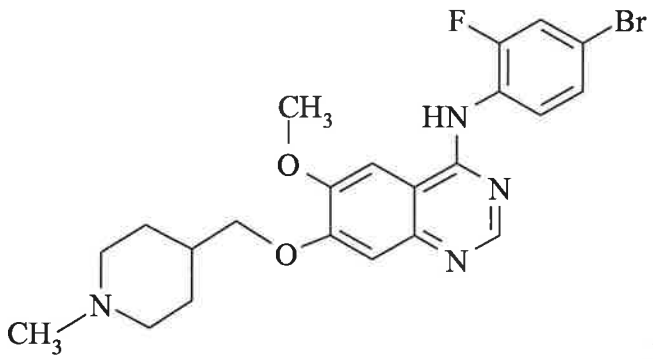
~~CHEMICAL PROCESS~~

The present invention relates to chemical processes for the manufacture of certain quinazoline derivatives, or pharmaceutically acceptable salts thereof. The invention also relates to processes for the manufacture of certain intermediates useful in the manufacture of the quinazoline derivatives and to processes for the manufacture of the quinazoline derivatives utilising said intermediates.

In particular, the present invention relates to chemical processes and intermediates useful in the manufacture of the compound 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline. This compound falls within the broad disclosure of WO 98/13354 and is exemplified in WO 01/32651, in Examples 2a, 2b and 2c.

The compound 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline is described herein by way of the Formula I:



I

and as ZD6474, the code number by which the compound is known. The compound ZD6474 is also known as Vandetanib and as Zactima™.

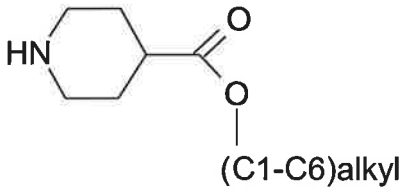
Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and

1-carboxylate, which is isolated as an oil. The 1-(*tert*-butoxycarbonyl)-4-hydroxymethylpiperidine is then reacted with toluene sulfonyl chloride and pyridine to provide the compound of the Formula II.

The routes disclosed in the prior art documents for the preparation of a compound of the Formula II are satisfactory for the synthesis of relatively small amounts of the compound. However, they all require each of the intermediates to be isolated and, therefore, include multiple isolation and/or purification steps. This results in a satisfactory overall yield of the compound of the Formula II on the small scale used. However, the routes disclosed in the prior art documents are unsuitable for use on a manufacturing scale because they include multiple isolation and/or purification steps, which cannot be conducted efficiently on a manufacturing scale. In particular, the routes disclosed in the prior art documents are unsuitable for use in the manufacture of a high purity pharmaceutical product.

There is, therefore, a need for a more efficient synthesis of a compound of the Formula II suitable for use to make larger quantities of that compound. Preferably, the new synthesis should not involve costly and time-consuming isolation and/or purification procedures. Thus, the new synthesis should reduce the number of isolation and/or purification procedures required, thereby reducing costs and time of manufacture. Preferably, the new synthesis should minimise the number of solvents used throughout the process, which improves environmental performance and provides the opportunity for solvent recovery. Preferably, the new synthesis should also provide a robust and reliable method of isolating the compound of the Formula II and consistently should provide high quality compound of the Formula II, for example so as to satisfy the regulatory requirements for the introduction of starting materials into the production of pharmaceutical products.

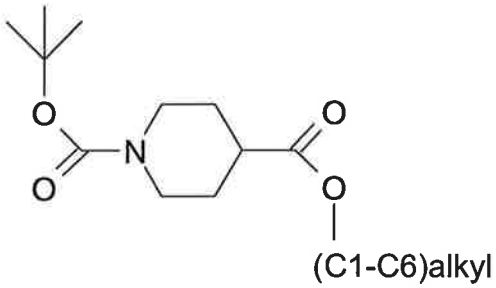
~~According to a first aspect of the present invention, there is provided a~~ A process for the manufacture of a compound of the Formula IIa from a (C1-C6)alkyl-4-piperidinecarboxylate compound of the Formula III:



III;

~~which process~~ may comprises the steps of:

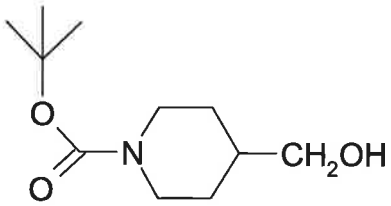
(a) reacting the (C1-C6)alkyl-4-piperidinecarboxylate compound of the Formula III with di-*tert*-butyl dicarbonate in the presence of toluene or xylene to form a first mixture comprising toluene or xylene, *tert*-butanol and a compound of the Formula IV:



IV;

(b) substantially removing the *tert*-butanol from the first mixture;

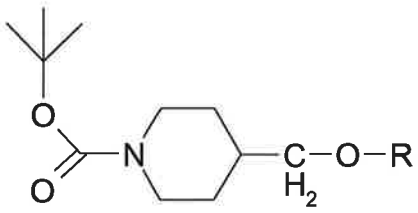
(c) reacting the compound of the Formula IV with a suitable reducing agent *in situ* in the presence of toluene or xylene to form a second mixture comprising toluene, reduction by-products including alcohol by-products and a compound of the Formula V:



V;

(d) substantially removing the alcohol by-products from the second mixture; and

(e) reacting the compound of the Formula V with a suitable sulphonating agent *in situ* to form a sulphonate ester in the presence of a suitable base and toluene to form the compound of the Formula IIa.



IIa

wherein R is a suitable sulphonate ester such as mesylate, esylate , besylate or tosylate. In one embodiment the sulphonating agent is tosyl chloride.

For avoidance of doubt the term '*in situ*' means that the reaction was performed without isolation of the reactants from the previous process step.

The process for the manufacture of a compound of the formula IIa ~~of the first aspect of the present invention~~ is advantageous in that it allows a compound of the Formula IIa to be made in high quality and high yield on a larger scale. Typically, each of the steps of the process ~~of the first aspect of the present invention~~ proceeds in greater than 95% yield.

All steps of the process for the manufacture of a compound of the formula IIa ~~of the first aspect of the present invention~~ are conducted in toluene or xylene as the solvent. In another embodiment all the steps ~~of the first aspect of the present invention~~ are conducted in toluene. This allows the process to be conducted as a continuous process without isolation and/or purification of the intermediate compounds of the Formulae IV and V. This significantly reduces the time and cost of manufacturing the compound of the Formula IIa on a larger scale. The use of a single solvent such as toluene or xylene may also allow for solvent recycling, which increases the efficiency of the process and provides environmental benefits. The use of toluene or xylene as the solvent also allows for the efficient and convenient removal of reactive by-products (such as alcohols), for example by distillation. The presence of such reactive by-products could lead to impurities in the compound of the Formula IIa if not removed at the appropriate time.

Additionally, the use of toluene or xylene as the solvent in the process for the manufacture of a compound of the formula IIa ~~of the first aspect of the present invention~~ allows for the convenient isolation of the compound of the Formula IIa by crystallisation. The compound of the Formula IIa may, for example, be isolated in greater than 99.5% purity by crystallisation directly from the reaction mixture without the need for further purification. This is advantageous, for example when the compound of the Formula IIa is to be introduced at a late stage into the production of a

The distillation in step (d) also typically substantially removes any water that is present. This again allows for the correct stoichiometry of the reagents in step (e) of the process because any water that is not removed is likely to react with the sulphonating agent in step (e), thereby reducing the amount of the sulphonating agent available for the desired reaction with the compound of the Formula V. By the term "substantially removed" we mean that less than 20 mol% of water remains after the distillation.

As the skilled person would appreciate, it is typically necessary to quench the reaction mixture in step (c) to remove any unreacted reducing agent that is present before the reaction in step (e) is conducted. Typically, the quench step also removes some of the reduction by-products listed above, for example the aluminium salts and some, but not all, of the alcohol by-products. Suitable quenching agents may in general be chosen from any agent that is described in the literature and/or that is known to the skilled person. For example, when the reducing agent used in step (c) is sodium bis(2-methoxyethoxy)aluminium hydride, the quenching agent typically may be an aqueous solution of potassium sodium tartrate (also known as Rochelle salt). Typically, the resulting aqueous phase (containing the quenched reducing agent) is then removed by separation. The quench step is conducted before the distillation in step (d).

A suitable base for use in step (e) is a tertiary amine base, for example triethylenediamine.

The reaction of step (e) is carried out at a temperature in the range, for example, of from 15 to 45°C, more conveniently in the range of from 25 to 35°C.

As the skilled person would appreciate, it is typically necessary to quench the reaction mixture in step (e) to remove any unreacted sulphonating agent that is present. Suitable quenching agents may in general be chosen from any agent that is described in the literature and/or that is known to the skilled person. For example, a suitable quenching agent may be a base such as sodium hydroxide or potassium carbonate.

~~In one aspect, t~~ The process for the manufacture of a compound of the Formula II may further include the step (f) of isolating and/or purifying the compound of the Formula II. The step (f) may comprise any suitable steps or procedures for isolating the desired product that are described in the literature and/or that are known to the skilled person. Particular steps that would be of use would provide high quality and high purity product.

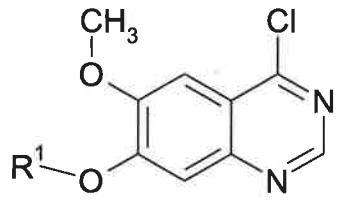
preparation of the hydrochloride salt of 7-benzyloxy-4-chloro-6-methoxyquinazoline is disclosed in Example 4 of WO 97/32856.

WO 98/10767 discloses a route for the preparation of 6,7-disubstituted 4-anilinoquinazoline compounds. The route involves the reaction of a 6,7-disubstituted quinazolinone compound with a chlorinating agent and a catalyst in the absence of a solvent or with a chlorinating agent in the presence of a trapping agent to provide a 6,7-disubstituted 4-chloroquinazoline compound. The 6,7-disubstituted 4-chloroquinazoline compound is then reacted with a substituted aniline compound, optionally in the presence of a suitable base, to provide a hydrochloride salt of the 6,7-disubstituted 4-anilinoquinazoline compound, which may then be converted to the free base. There is no disclosure in WO 98/10767 of 7-benzyloxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline or of a process for its preparation.

The routes disclosed in the prior art documents for the preparation of a compound of the Formula VI are satisfactory for the synthesis of relatively small amounts of the compound. However, they all require the isolation and/or purification of intermediate compounds. This results in a satisfactory, but not high, overall yield of the compound of the Formula VI.

There is, therefore, a need for a more efficient synthesis of a compound of the Formula VI suitable for use to make larger quantities of that compound. Preferably, the new synthesis should not involve costly and time-consuming isolation and/or purification procedures. Thus, the new synthesis should reduce the number of isolation and/or purification procedures required, thereby reducing costs and time of manufacture. The new synthesis should also allow for effective isolation of the compound of the Formula VI in a crystalline form in high purity and yield, which crystalline form should have good filtration characteristics.

According to a <u>first</u> ~~second~~ aspect of the present invention, there is provided a process for the manufacture of a compound of the Formula VI:



VIII; and

(h) reacting the compound of the Formula VIII with 4-bromo-2-fluoroaniline *in situ* in the presence of the solvent used in step (g) to form a hydrochloride salt of the compound of the Formula VI;

and whereafter the compound of the Formula VI obtained in the form of the hydrochloride salt may be converted into the free base or into the form of an alternative salt, if necessary.

The term 'acid labile protecting group' refers to groups which are readily removed under acidic conditions. Suitable methods for protection are those known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Suitable protecting groups at R^1 include benzyl, substituted benzyl (for example C_{1-4}alkoxybenzyl and C_{1-4}alkybenzyl), *tert*-butyl, 1, 1-dimethyl-1-ethylmethyl, allyl, substituted allyl (such as C_{1-4}alkylallyl) or methoxyethoxymethyl. In another embodiment R^1 is benzyl.

The process of the <u>first</u> ~~second~~ aspect of the invention is advantageous in that it allows a compound of the Formula VI to be made in high purity and high yield on a larger scale. Typically, each of the steps of the process of the <u>first</u> ~~second~~ aspect of the present invention proceeds in greater than 90% yield.

A suitable solvent for step (g) is selected from an aryl alkyl ether, such as anisole, a dialkyl ether such as 1,2-dimethyl ether, a halo substituted benzene such as chlorobenezene or trifluorotoluene or an alkyl substituted benzene such as xylene, ethyl benzene or toluene. In one embodiment of the invention the solvent for step (g) is anisole or toluene. In another embodiment of the invention the solvent for step (g) is toluene.

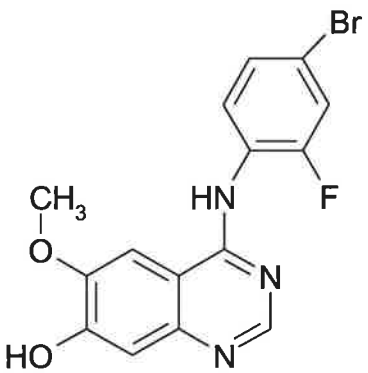
Steps (g) and (h) are both conducted in the same solvent, which solvent is selected from a suitable solvent as described above. This allows the process to be conducted as a continuous process without isolation and/or purification of the intermediate compound of the Formula VIII. This significantly reduces the time and cost of manufacturing the

As discussed above, WO 98/10767 discloses a route for the preparation of 6,7-disubstituted 4-anilinoquinazoline compounds. There is no disclosure in WO 98/10767 of 7-hydroxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline or of a process for its preparation.

The routes disclosed in the prior art documents for the preparation of a compound of the Formula IX are satisfactory for the synthesis of relatively small amounts of the compound. However, they all require the isolation and/or purification of intermediate compounds. This results in a satisfactory, but not high, overall yield of the compound of the Formula IX.

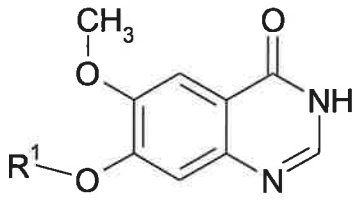
There is, therefore, a need for a more efficient synthesis of the compound of the Formula IX suitable for use to make larger quantities of that compound. Preferably, the new synthesis should not involve costly and time-consuming purification procedures. Thus, the new synthesis should reduce the number of isolation and/or purification procedures required, thereby reducing costs and time of manufacture. Preferably, the new synthesis should minimise the number of solvents used throughout the process, which improves environmental performance and provides the opportunity for solvent recovery. The new synthesis should also enable effective crystallisation of the compound of the Formula IX in a crystalline form with good filtration characteristics and in high purity and yield.

According to a second ~~third~~ aspect of the present invention, there is provided a process for the manufacture of 7-hydroxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline, a compound of the Formula IX:



IX

from a compound of the Formula VII:



VII

wherein R^1 is an acid labile protecting group

which process comprises the steps of:

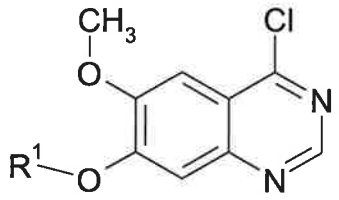
(g) reacting the compound of the Formula VII with a suitable chlorinating agent in the presence of a suitable base and a suitable solvent, wherein the reaction is carried out by:

(g-1) adding a mixture of the compound of the Formula VII and the base in the solvent to a mixture of the chlorinating agent in the solvent at a temperature in the range of from 60 to 110°C, conveniently 60 to 80°C over a period of about 60 minutes; or

(g-2) adding the chlorinating agent to a mixture of the compound of the Formula VII and the base in the solvent at ambient temperature over a period of about 15 minutes and then heating the reaction mixture over a period of about 90 minutes to a temperature in the range of from 70 to 90°C and stirring the reaction mixture at that temperature for about 1 hour; or

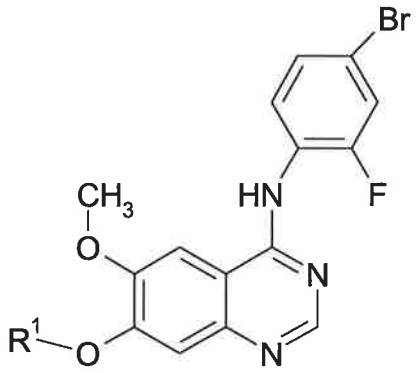
(g-3) adding the chlorinating agent to a mixture of the compound of the Formula VII and the base in the solvent at a temperature in the range of from 60 to 110°C, conveniently 70 to 90°C over a period of about 15 minutes,

to form a compound of the Formula VIII:



VIII;

(h) reacting the compound of the Formula VIII with 4-bromo-2-fluoroaniline *in situ* in the presence of the solvent used in step (g) to form a compound of the Formula VI;



VI; and

(j) removing R^1 from the compound of the Formula VI *in situ* in the presence of the solvent used in steps (g) and (h) to form the compound of the Formula IX or a salt thereof;

and whereafter the compound of the Formula IX obtained in the form of the free base may be converted into a salt form and the compound of the Formula IX obtained in the form of a salt may be converted into the free base or into the form of an alternative salt, if necessary.

The process of the second ~~third~~ aspect of the invention is advantageous in that it allows the compound of the Formula IX to be made in high purity and high yield on a larger scale. Typically, each of the steps of the process of the second ~~third~~ aspect of the present invention proceeds in at least 95% yield. Typically, the process of the second ~~third~~ aspect of the present invention produces the compound of the Formula IX in at least 85% yield.

Steps (g), (h) and (j) are all conducted in the same solvent, which solvent is selected from an aryl alkyl ether, such as anisole, a dialkyl ether such as 1,2-dimethyl ether, a halo substituted benzene such as chlorobenezene or trifluorotoluene or an alkyl substituted benzene such as xylene, ethyl benzene or toluene. In one embodiment of the invention the solvent for step (g), (h) and (j) is anisole or toluene. In another embodiment of the invention the solvent for step (g), (h) and (j) is toluene. This allows the process to be conducted as a continuous process without isolation and/or purification of the intermediate compounds of the Formulae VIII and VI. This significantly reduces the time and cost of manufacturing the compound of the Formula IX on a larger scale. The use of a single solvent may allow for solvent recycling, which increases the efficiency of the process and provides environmental benefits. The use of these solvents as the reaction solvent is advantageous because these solvents minimise the formation of by-products that may be derived by dimerisation of the compound of the Formula VII, as discussed above.

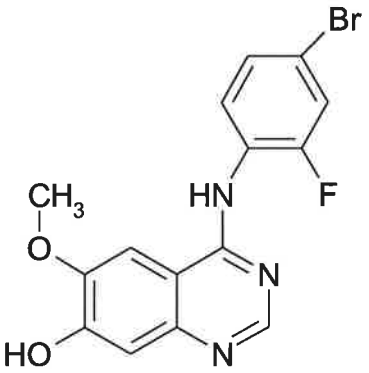
ether, such as anisole, a dialkyl ether such as 1,2-dimethoxyethane, a halo substituted benzene such as chlorobenezene or trifluorotoluene or an alkyl substituted benzene such as xylene, ethyl benzene or toluene. In one embodiment of the invention the solvent for step (j) is anisole or toluene. In another embodiment of the invention the solvent for step (j) is toluene. Thereby, the compound of the Formula IX may be manufactured from a compound of the Formula VII in a one-pot procedure.

A suitable method of removing the acid labile protecting group *in situ* in step (j) is by reaction with an acid, such as trifluoroacetic acid. Optionally, a second acid (such as hydrogen chloride or hydrogen bromide) may be used in addition to, or as a replacement for, the trifluoroacetic acid. When an acid is used to remove R^1 in step (j), then the compound of the Formula IX is obtained in the form of a salt. The use of trifluoroacetic acid in step (j) is advantageous because it allows for easy isolation of the compound of the Formula IX, for example by crystallisation from the trifluoroacetic acid by addition of water and cooling or by addition of and aqueous alkali metal base such as potassium hydroxide, sodium hydroxide, sodium acetate, potassium acetate, more preferably potassium hydroxide followed by water and cooling. The crystalline solid so formed may be collected by any conventional method, for example by filtration.

The reaction of step (j) is carried out at a temperature in the range of from 60 to 90°C, conveniently 60 to 80°C, more conveniently in the range of from 70 to 75°C.

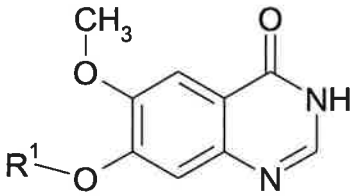
In one aspect of the invention, following step (j) of the process, the compound of the Formula IX is isolated and/or purified. Any suitable steps or procedures for isolating and/or purifying the desired product that are described in the literature and/or that are known to the skilled person may be used. Particular steps that would be of use would provide high quality and high purity product. For example, the compound of the Formula IX may be isolated from trifluoroacetic acid by addition of water and cooling or more preferably by addition of and aqueous alkali metal base such as potassium hydroxide and water and cooling, as discussed above.

According to a <u>third</u> ~~fourth~~ aspect of the present invention, there is provided a process for the manufacture of 7-hydroxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline, a compound of the Formula IX:



IX

from a compound of the Formula VII:



VII

where R^1 is an acid labile protecting group

which process comprises the steps of:

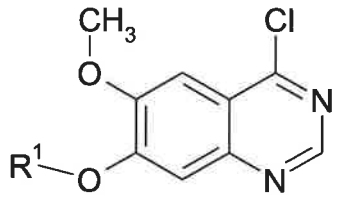
(g) reacting the compound of the Formula VII with a suitable chlorinating agent in the presence of a suitable base and a suitable solvent selected from toluene and anisole, wherein the reaction is carried out by:

(g-1) adding a mixture of the compound of the Formula VII and the base in the solvent to a mixture of the chlorinating agent in the solvent at a temperature in the range of from 60 to 110°C, conveniently 60 to 80°C over a period of about 60 minutes; or

(g-2) adding the chlorinating agent to a mixture of the compound of the Formula VII and the base in the solvent at ambient temperature over a period of about 15 minutes and then heating the reaction mixture over a period of about 90 minutes to a temperature in the range of from 70 to 90°C and stirring the reaction mixture at that temperature for about 1 hour; or

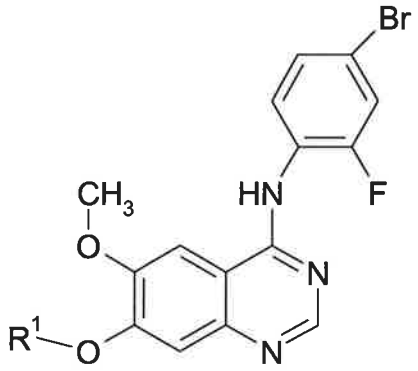
(g-3) adding the chlorinating agent to a mixture of the compound of the Formula VII and the base in the solvent at a temperature in the range of from 60 to 110°C, conveniently 70 to 90°C over a period of about 15 minutes,

to form a compound of the Formula VIII:



VIII;

(h) reacting the compound of the Formula VIII with 4-bromo-2-fluoroaniline *in situ* in the presence of the solvent used in step (g) to form the compound of the Formula VI:



VI;

(i) isolating the compound of the Formula VI; and

(k) removing R^1 from the compound of the Formula VI to form the compound of the Formula IX or a salt thereof;

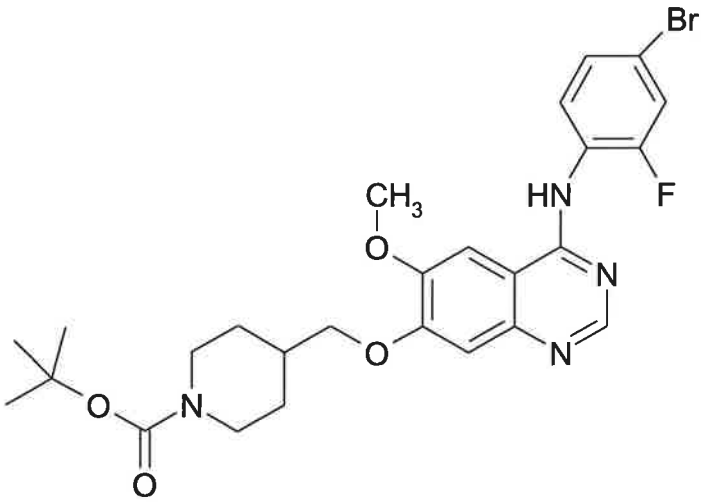
and whereafter the compound of the Formula IX obtained in the form of the free base may be converted into a salt form and the compound of the Formula IX obtained in the form of a salt may be converted into the free base or into the form of an alternative salt such a trifluoroacetic acid or hydrochloride salt, if necessary.

The process of the third ~~fourth~~ aspect of the invention is advantageous in that it allows a compound of the Formula IX to be made in high purity and high yield on a larger scale.

Steps (g) and (h) are both conducted in the same solvent, which solvent is selected from an aryl alkyl ether, such as anisole, a dialkyl ether such as 1,2-dimethyl ether, a halo substituted benzene such as chlorobenezene or trifluorotoluene or an alkyl substituted benzene such as xylene, ethyl benzene or toluene. In one embodiment of the invention the solvent for step (g) and (h) is anisole or toluene. In another embodiment of the invention the solvent for step (g) and (h) is toluene. This allows the process to be conducted as a continuous process without isolation and/or purification of the intermediate compound of the Formula VIII. This significantly reduces the time and cost of manufacturing the

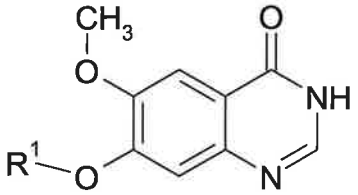
The routes disclosed in the prior art documents for the preparation of a compound of the Formula X are satisfactory for the synthesis of relatively small amounts of the compound. However, there is a need for a more efficient synthesis of the compound of the Formula X suitable for use to make larger quantities of that compound. Preferably, the new synthesis should not involve costly and time-consuming purification procedures. Thus, the new synthesis should reduce the number of isolation and/or purification procedures required, thereby reducing costs and time of manufacture. Preferably, the new synthesis should minimise the number of solvents used throughout the process, which improves environmental performance and provides the opportunity for solvent recovery. The new synthesis should also provide the compound of the Formula X in a high purity and in a high yield.

According to a fourth ~~fifth~~ aspect of the present invention, there is provided a process for the manufacture of 7-(1-*tert*-butoxycarbonyl)piperidine-4-ylmethoxy)-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline, a compound of the Formula X:



X

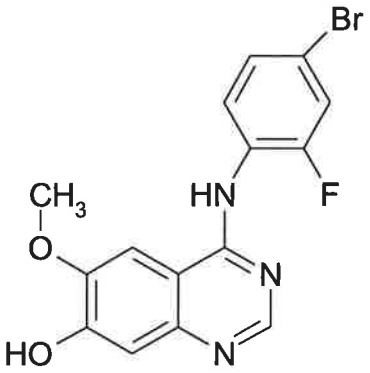
from a compound of the Formula VII:



VII;

where R^1 is an acid labile protecting group

which process comprises the steps of converting the compound of the Formula VII to a compound of the Formula IX:



IX

by conducting a process as discussed above in relation to the second ~~third~~ or the third ~~fourth~~ aspect of the invention; and

(l) reacting the compound of the Formula IX with a compound of the Formula II as defined above in the presence of a suitable base to provide a compound of the Formula X or a salt thereof;

and whereafter the compound of the Formula X obtained in the form of the free base in either solvated or non-solvated forms may be converted into a salt form and the compound of the Formula X obtained in the form of a salt may be converted into the free base or into the form of an alternative salt, if necessary.

The process of the fourth ~~fifth~~ aspect of the invention is advantageous in that it allows the compound of the Formula X to be made in high purity and high yield on a larger scale. Typically the process of the fourth ~~fifth~~ aspect of the present invention proceeds in greater than 80% yield. The process of the fourth ~~fifth~~ aspect of the invention is also advantageous for at least the reasons discussed above in relation to the second ~~third~~ and third ~~fourth~~ aspects of the invention.

Typically, the compound of the Formula IX is isolated and/or purified before step (l) is conducted, for example using any suitable steps or procedures that are described in the literature and/or that are known to the skilled person as discussed above.

In another embodiment of the invention following the manufacture of the compound of the Formula IX in step (j) wherein R^1 is benzyl (or substituted benzyl) and when hydrogenation is used as the method of deprotection of the benzyl group, the compound is used directly in step (l) for manufacturing a compound of the Formula X. In other words, the compound of the Formula IX is not isolated as such but is used as a

solution or slurry in a suitable solvent such as N-methyl pyrrolidone, dimethylformamide or dimethylacetamide. In one embodiment of the invention the solvent for step (j) is N-methylpyrolidone. Thereby, the compound of the Formula X may be manufactured from a compound of the Formula VIII in a one-pot procedure.

A suitable base for use in step (l) is selected from sodium carbonate, sodium bicarbonate, potassium carbonate, sodium hydroxide, potassium tert-butanol, and potassium hydroxide.

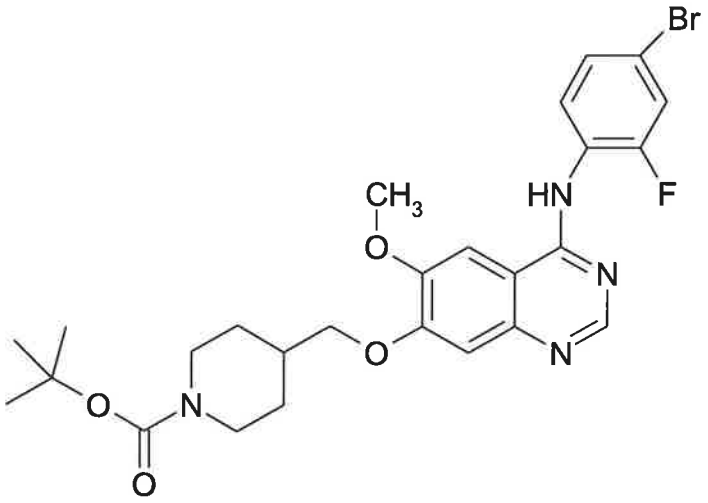
Step (l) may be conducted in any suitable solvent and at any suitable temperature.

When the base used in step (l) is selected from sodium carbonate and potassium carbonate, suitable solvents include, for example, *N*-methylpyrrolidone, *N*-ethylpyrrolidone, dimetylacetamide, dimethylsulphoxide, sulpholine, methylethyl ketone and *N*,*N*-dimethylformamide. In this aspect, step (l) typically may be conducted at a temperature in the range of from 60 to 120°C, conveniently 70 to 105°C, conveniently in the range of from 80 to 100°C, conveniently in the range 70-90°C, conveniently in the range of from 90 to 95°C. In a further embodiment in the range 75-85°C.

When the base used in step (l) is selected from sodium hydroxide and potassium hydroxide, suitable solvents include, for example, an aryl alkyl ether, such as anisole, a dialkyl ether such as 1,2-dimethoxyethane, a halo substituted benzene such as chlorobenezene or trifluorotoluene or an alkyl substituted benzene such as xylene, ethyl benzene or toluene or acetonitrile. In one embodiment of the invention the solvent for step (l) is anisole or toluene. In another embodiment of the invention the solvent for step (l) is toluene. In this aspect, step (l) typically may be conducted at a temperature in the range of from 60 to 90°C, conveniently in the range of from 65 to 85°C, conveniently in the range of from 70 to 80°C. In this aspect, step (l) may conveniently be conducted by adding water, the base (such as sodium hydroxide or potassium hydroxide) and a suitable phase transfer catalyst in toluene to the reaction mixture. Suitable phase transfer catalysts include, for example, tetrabutylammonium bromide and Adogen® 464 (methyltrialkyl(C_{8-10}) ammonium chloride, CAS 63393-96-4).

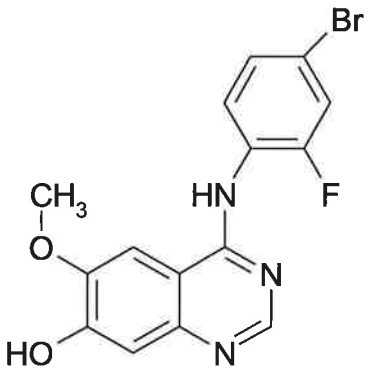
In one aspect, the process of the <u>fourth</u> ~~fifth~~ aspect of the invention may include the step (m) of isolating the compound of the Formula X. The step (m) may comprise any suitable steps or procedures for isolating the compound of the Formula X that are described in the literature and/or that are known to the skilled person.

According to a fifth ~~sixth~~ aspect of the present invention, there is provided a process for the manufacture of 7-(1-*tert*-butoxycarbonyl)piperidine-4-ylmethoxy)-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline, a compound of the Formula X:



X

from 7-hydroxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline, a compound of the Formula IX:



IX

(l) reacting the compound of the Formula IX with a compound of the Formula II as defined above in the presence of a suitable base to provide a compound of the Formula X or a salt thereof; and

(m) isolating the compound of the Formula X by:

(m-1) adding water and allowing crystallisation of the compound of the Formula X to occur, collecting the compound of the Formula X and washing the compound of the Formula X with water, followed by a solvent selected from ethyl acetate,

butyl acetate and acetonitrile at a temperature in the range of from 25 to 55°C, conveniently 45 to 55°C; or

(m-2) adding water and an alcohol selected from methanol, ethanol, isopropanol and n-propanol (particularly isopropanol) and allowing crystallisation of the compound of the Formula X to occur, collecting the compound of the Formula X and washing the compound of the Formula X with a mixture of water and the alcohol selected from methanol, ethanol, isopropanol and n-propanol, followed by a solvent selected from ethyl acetate, butyl acetate and acetonitrile at a temperature in the range of from 25 to 55°C, conveniently 25 to 55°C;

and whereafter the compound of the Formula X obtained in the form of the free base in either solvated or non solvated forms (or solvate of solvents from NMP, Ethyl Acetate or a mixture of both) may be converted into a salt form and the compound of the Formula X obtained in the form of a salt may be converted into the free base or into the form of an alternative salt, if necessary.

The process of the fifth ~~sixth~~ aspect of the invention is advantageous in that it allows the compound of the Formula X to be made in high purity and high yield on a larger scale. Typically, each of the steps of the process of the fifth ~~sixth~~ aspect of the present invention proceeds in greater than 80% yield.

The process provides for the efficient removal of any unreacted compound of the Formula IX, as well as of any impurities that are routinely formed during step (l) of the process. Such impurities include those formed by reaction of the compound of the Formula II at the 1-position nitrogen atom in the quinazoline ring instead of at the desired position at the hydroxy substituent.

A suitable base for use in step (l) is selected from sodium carbonate, sodium hydroxide, potassium hydroxide and potassium carbonate.

Step (l) may be conducted in any suitable solvent or at any suitable temperature.

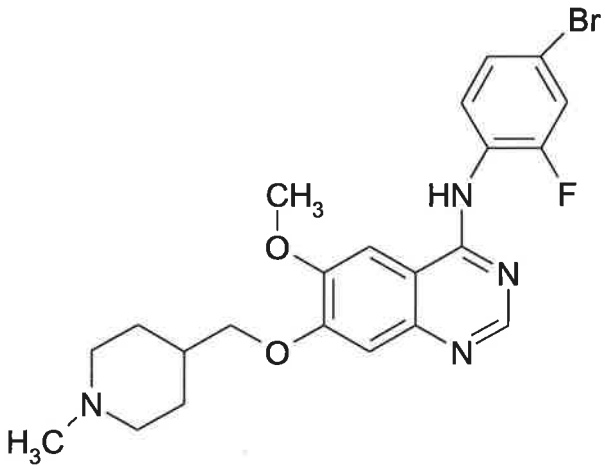
When the base used in step (l) is selected from sodium carbonate and potassium carbonate, suitable solvents include, for example, *N*-methylpyrrolidone, *N*-ethylpyrrolidone and *N*,*N*-dimethylformamide. In this aspect, step (l) typically may be conducted at a temperature in the range of from 70 to 105°C, conveniently of from 80 to 100°C, conveniently of from 90 to 95°C.

The steps (m-1) and (m-2) are advantageous because they are efficient at removing unreacted compound of the Formula IX, as well as impurities that are routinely formed during step (l) of the process. Such impurities include those formed by reaction of the compound of the Formula II at the 1-position nitrogen atom in the quinazoline ring instead of at the desired position at the hydroxy substituent.

In steps (m-1) and (m-2), the crystalline solid so formed may be collected by any conventional method, for example by filtration. The collected crystalline solid may, if necessary, then be washed with the appropriate solvent and may then be dried.

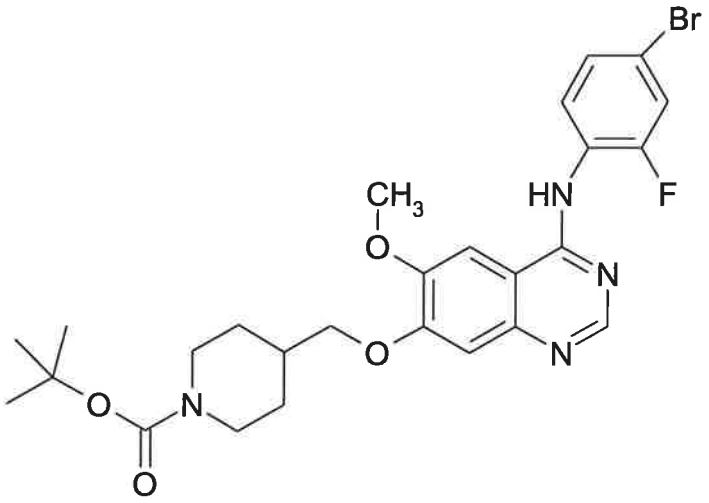
The compound of the Formula II used in step (l) of the processes of the fourth ~~fifth~~ and fifth ~~sixth~~ aspects of the invention may be obtained by any literature or conventional method. In one aspect of the invention, the compound of the Formula II used in step (l) of the fourth ~~fifth~~ or fifth ~~sixth~~ aspect of the invention is prepared according to the process ~~of the first aspect of the invention,~~ as discussed above.

According to a sixth ~~seventh~~ aspect of the invention, there is provided a process for the manufacture of ZD6474:



ZD6474

from a compound of the Formula X:



X

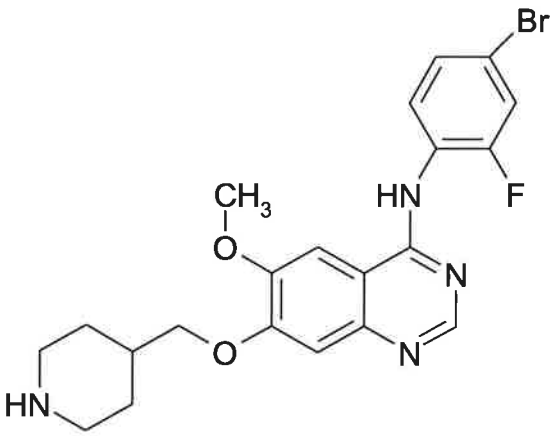
which process comprises the steps of:

(n) reacting the compound of the Formula X with formic acid and formaldehyde or a polymer of formaldehyde, conveniently in water at a temperature in the range of from 70 to 95°C, conveniently 70 to 90°C to form a formic acid salt of ZD6474;

(o) adding an inert organic solvent selected from tetrahydrofuran, butyronitrile and methanol and a suitable base so as to form the free base of ZD6474;

whereafter the ZD6474 obtained in the form of the free base may be converted into a pharmaceutically acceptable salt, if necessary.

In step (n) of the process of the sixth ~~seventh~~ aspect of the invention, the reaction proceeds via a transient intermediate, which intermediate is 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline, a compound of the Formula XI:



XI

The process of the sixth ~~seventh~~ aspect of the invention is advantageous in that it allows the ZD6474 to be made in high purity and high yield on a larger scale. Typically, each of the steps of the process of the sixth ~~seventh~~ aspect of the present invention proceeds in greater than 90% yield.

The compound of the Formula X used in step (n) of the process of the sixth ~~seventh~~ aspect of the invention may be obtained by any literature or conventional method (for example, as described in WO 01/32651 discussed previously). Alternatively, in one aspect of the invention, the compound of the Formula X used in step (n) of the sixth ~~seventh~~ aspect of the invention is prepared according to the process of the fourth ~~fifth~~ or the fifth ~~sixth~~ aspect of the invention, as discussed above.

Step (n) is conducted at a temperature in the range of from 70 to 95°C, conveniently 70 to 90°C, conveniently in the range of from 75 to 85°C, more conveniently at about 80°C.

Preferably, step (n) is conducted under an inert atmosphere, for example under a nitrogen atmosphere. This is advantageous because the process of step (n) may produce hydrogen gas and carbon monoxide as a by-product, which hydrogen gas must be removed from the reaction vessel in a safe and effective manner.

In step (n), the formic acid salt of ZD6474 is produced. This salt is converted to the free base of ZD6474 in step (o) of the process.

In step (n) examples of polymers of formaldehyde include paraformaldehyde and s-trioxane (1,3,5 trioxane).

A suitable inert organic solvent for use in step (o) is selected from tetrahydrofuran, butyronitrile and methanol (particularly tetrahydrofuran or methanol). The inert organic solvent is added to the reaction mixture after the completion of the reaction in step (n). As the skilled person would appreciate, it may be necessary to cool the reaction mixture before the inert organic solvent is added.

A suitable base for use in step (o) is sodium hydroxide or potassium hydroxide (particularly potassium hydroxide). The addition of a base in step (o) converts the formic acid salt of ZD6474 to the free base of ZD6474.

When the inert organic solvent used in step (o) is selected from tetrahydrofuran and butyronitrile, the ZD6474 product is effectively transferred from the aqueous phase to the organic phase. This is because, once made, the free base of ZD6474 is preferentially

soluble in the inert organic solvent (whereas the formic acid salt of ZD6474 is soluble in the aqueous phase). When the inert organic solvent used in step (o) is methanol, the free base of ZD6474 typically crystallises directly from the reaction mixture. When the base is potassium hydroxide this is particularly advantageous as the formate salt are completely soluble in the methanol solvent and don't contaminate the isolated compound ZD6474. This also provide a crystalline compound with good filtration characteristics. (this can be isolated as either the anhydrate form, a methanoate form or a mixed methanoate hydrate). Thus, step (o) of the process is advantageous because it aids and simplifies the isolation and purification of the ZD6474 product, particularly when the process is conducted on a larger scale.

Step (o) is conducted at a temperature in the range of from 30 to 70°C, conveniently in the range of from 40 to 65°C, more conveniently in the range of from 40 to 60°C.

In one aspect, the process of the sixth ~~seventh~~ aspect of the invention may include the step (p) of isolating and/or purifying the free base of the ZD6474. The step (p) may comprise any suitable steps or procedures for isolating and/or purifying the free base of ZD6474 that are described in the literature and/or that are known to the skilled person. Alternatively, for example, when the inert organic solvent used in step (o) is selected from tetrahydrofuran and butyronitrile, the step (p) may comprise the steps of:

(p-1) separating and removing the aqueous phase from the organic phase;

(p-2) charging n-butyl acetate to the organic phase;

(p-3) washing the organic phase with water and separating and removing the aqueous phase from the organic phase;

(p-4) adding tetrahydrofuran and n-butyl acetate to the organic phase;

(p-5) distilling the organic phase so as to substantially remove the water and the tetrahydrofuran and to provide a suspension of ZD6474 in predominately n-butyl acetate;

(p-6) allowing crystallisation of the ZD6474 to complete; and

(p-7) collecting the ZD6474.

The steps (p-1), (p-2) and (p-3) are advantageous because they readily and easily remove formic acid salts and residual formaldehyde or polymer of formaldehyde from the ZD6474 product dissolved in the organic phase.

In one aspect, the steps (p-1), (p-2), (p-3) and (p-4) are each conducted at a temperature in the range of from 50 to 65°C, conveniently in the range of from 55 to 65°C, more conveniently of about 60°C.

Typically, steps (p-1), (p-2) and (p-3) may each be repeated twice before step (p-4) is conducted.

Step (p-5) substantially removes any water and tetrahydrofuran that is present in the organic phase that has been separated from the aqueous phase in steps (p-1) and (p-3). The distillation is conducted so as to provide a solvent composition that contains about 90% w/w n-butyl acetate. In other words, the solution of ZD6474 in predominantly n-butyl acetate is a solution of ZD6474 in a solvent composition that contains about 90% w/w n-butyl acetate. Typically, the distillation is conducted until an internal temperature in the range of from 90 to 110°C, conveniently 90 to 104°C is achieved conveniently in the range of from 100-110°C. The distillation in step (p-5) is conveniently conducted at atmospheric pressure (or reduced pressure but more conveniently at ambient pressure).

For the avoidance of doubt in (p-6) where it refers to 'allowing crystallisation of the ZD6474 to complete' this means that the crystallisation process has completed at the conditions used, it does not mean that 100% of the ZD6474 in the reaction mixture has crystallised.

An alternative step (p) of isolating and/or purifying the free base of ZD6474, when the inert organic solvent used in step (o) is tetrahydrofuran, may comprise the steps of:

(p-8) adding water to the ZD6474 solution in the organic phase obtained after step (p-1) so as to allow crystallisation of the ZD6474 to occur; and

(p-9) collecting the ZD6474.

In each of the above isolation steps, the crystalline solid so formed may be collected by any conventional method, for example by filtration. The collected crystalline solid may, if necessary, then be purified further, and may then be dried.

The step (p) of isolating the ZD6474 product is advantageous because it provides ZD6474 in a high yield (for example typically in greater than 90% yield) and a high purity (for example typically in greater than 99% purity). In addition, the step (p) provides a form of ZD6474 that is easily filterable on a larger scale.

In another aspect of the present invention, the ZD6474 prepared according to the process of the sixth ~~seventh~~ aspect of the invention as discussed above may be further purified.

The further purification of ZD6474 may comprise any suitable steps or procedures for isolating and/or purifying ZD6474 that are described in the literature and/or that are known to the skilled person. Alternatively, the further purification of the ZD6474 may comprise the steps of heating a suspension of the ZD6474 as prepared in the process of the sixth ~~seventh~~ aspect of the present invention in a mixture of tetrahydrofuran, water and butyl acetate to reflux, cooling the resulting mixture to a temperature in the range of from 50 to 65°C (conveniently of about 60°C), separating the aqueous and organic phases and filtering the organic phase. The filtrate may then be combined with further tetrahydrofuran and butyl acetate and the resulting mixture heated to a temperature in the range of 90 to 110°C, conveniently 90 to 110°C (conveniently in a range of from 100 to 110°C) before being cooled to a temperature in the range of from 40 to -10°C, conveniently 25 to 0°C (conveniently in the range of from 0 to 10°C, more conveniently of about 5°C, in a further embodiment at a temperature of about 25 °C) to provide a slurry of ZD6474. The ZD6474 may then be collected by any conventional method, for example by filtration, and optionally washed with ethyl acetate. This is advantageous because the described process reduces the level of water at the end of the distillation to below 1% thus ensuring that the anhydrrous form of ZD6474 is produced.

Alternatively, for example, when the inert organic solvent used in step (o) is tetrahydrofuran, the step (p) may comprise the steps of:

(p-1) separating and removing the aqueous phase from the organic phase;

(p-2) filtering the organic phase;

(p-3) charging n-butyl acetate to the organic phase;

(p-4) washing the organic phase with water and separating and removing the aqueous phase from the organic phase;

(p-5) adding tetrahydrofuran and n-butyl acetate to the organic phase;

(p-6) distilling the organic phase so as to substantially remove the water and the tetrahydrofuran and to provide a suspension of ZD6474 in predominately n-butyl acetate;

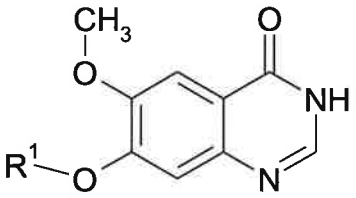
(p-7) cooling and charging additional tetrahydrofuran; and

(p-8) allowing crystallisation of the ZD6474 to complete; and

(p-9) collecting the ZD6474.

The step (p-7) is advantageous because it improves the quality of the product obtained by solubilising the impurities in the mother liquors. This allows the telescoping of the production of the Crude API (Active Pharmaceutical Ingredient) with the isolation of the purified API in a single step.

According to a seventh ~~n eighth~~ aspect of the present invention, there is provided a process for the manufacture of ZD6474 from a compound of the Formula VII:



VII

which process comprises the steps of:

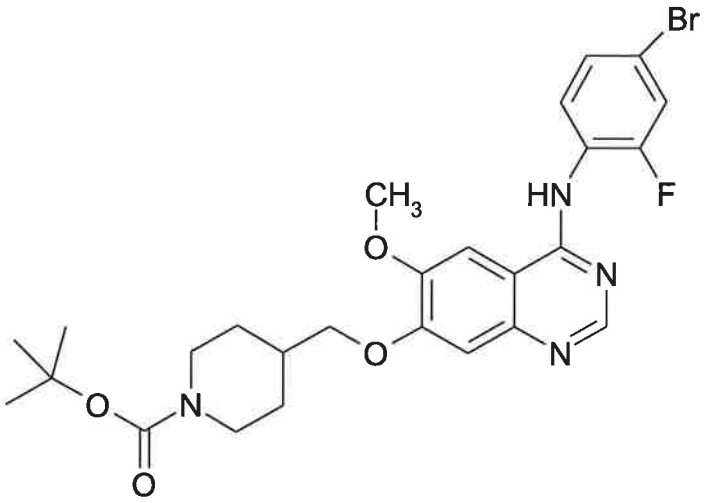
(g) reacting the compound of the Formula VII with a suitable chlorinating agent in the presence of a suitable base and a solvent selected from chlorobenezene, trifluorotoluene, xylene, ethyl benzene, toluene & anisole more specifically anisole and toluene, wherein the reaction is carried out by:

(g-1) adding a mixture of the compound of the Formula VII and the base in the solvent to a mixture of the chlorinating agent in the solvent at a temperature in the range of from 60 to 90°C, conveniently 60 to 80°C over a period of about 60 minutes; or

(g-2) adding the chlorinating agent to a mixture of the compound of the Formula VII and the base in the solvent at ambient temperature over a period of about 15 minutes and then heating the reaction mixture over a period of about 90 minutes to a temperature in the range of from 70 to 90°C and stirring the reaction mixture at that temperature for about 1 hour; or

(g-3) adding the chlorinating agent to a mixture of the compound of the Formula VII and the base in the solvent at a temperature in the range of from 60 to 110°C, conveniently 70 to 90°C over a period of about 15 minutes,

to form a compound of the Formula VIII:



X;

(n) reacting the compound of the Formula X with formic acid and formaldehyde or a polymer of formaldehyde conveniently in water at a temperature in the range of from 70 to 90°C to form the formic acid salt of ZD6474; and

(o) adding an inert organic solvent selected from tetrahydrofuran, butyronitrile and methanol and a suitable base so as to form the free base of ZD6474; and optionally

(p) further purifying ZD6474 in a mixture of tetrahydrofuran, water and butyl acetate to provide a required crystalline anhydrous form suitable for tablet manufacture.

whereafter the ZD6474 obtained in the form of the free base may be converted into a pharmaceutically acceptable salt form, if necessary.

The process of the seventh ~~eighth~~ aspect of the invention is advantageous in that it allows the ZD6474 to be made in high purity and high yield on a larger scale. Typically, each of the steps of the process of the seventh aspect of the present invention proceeds in greater than 90% yield.

Preferred aspects of the process of the seventh ~~eighth~~ aspect of the invention are as set out above in relation to individual steps as described in the first, second, third, fourth, fifth, and sixth ~~and seventh~~ aspects of the present invention. In particular, preferred aspects of the process of the seventh ~~eighth~~ aspect of the invention are as set out above, for example, in relation to individual steps of the second, fourth ~~third,~~ fifth, and/or sixth ~~and/or seventh~~ aspects of the present invention.

Conveniently, steps (g), (h) and (j) of the process of the seventh ~~eighth~~ aspect of the present invention are all conducted in toluene as the solvent and triethylamine as the base.

Conveniently, a suitable method of removing the benzyl group *in situ* in step (j) of the process of the seventh ~~eighth~~ aspect of the present invention, wherein R^1 is benzyl, is by reaction with trifluoroacetic acid.

Conveniently, the base used in step (l) of the process of the seventh ~~eighth~~ aspect of the present invention is potassium carbonate and the suitable solvent is *N*-methylpyrrolidone.

The process of the seventh ~~eighth~~ aspect of the present invention typically may include the step (m) of isolating the compound of the Formula X before steps (n) and (o) are conducted. Conveniently, the step (m) may be conducted as hereinbefore described.

Conveniently, a suitable base for use in step (o) of the seventh ~~eighth~~ aspect of the present invention is potassium hydroxide.

Conveniently, a suitable solvent for use in step (o) of the seventh ~~eighth~~ aspect of the present invention is methanol.

The process of the seventh ~~eighth~~ aspect of the present invention may include the step (p) of isolating and/or purifying the free base of the ZD6474. The step (p) may be conducted as hereinbefore described.

The invention is illustrated hereinafter by means of the following non-limiting Examples and Data in which, unless otherwise stated:-

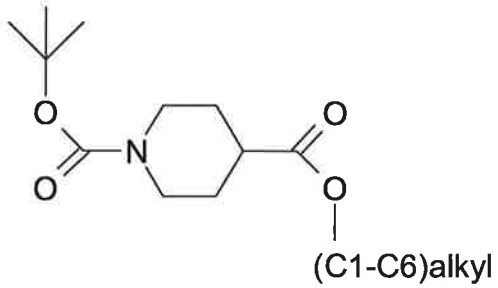
(i) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) yields are given for illustration only and are not necessarily the maximum attainable;

(iii) melting points are uncorrected and were determined using a Mettler DSC820e;

(iv) the structures of the end-products were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet; all samples run on a Bruker DPX 400 MHz at 300K in the solvent indicated, 16 scans, pulse repetition time 10 seconds;

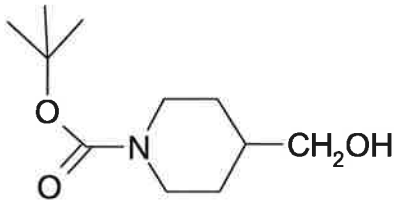
(v) intermediates were not generally fully characterised and purity was assessed by NMR analysis;



IV;

(b) substantially removing the *tert*-butanol from the first mixture;

(c) reacting the compound of the Formula IV with a suitable reducing agent *in situ* in the presence of toluene or xylene to form a second mixture comprising toluene or xylene, reduction by-products including alcohol by-products and a compound of the Formula V:



V;

(d) substantially removing the alcohol by-products from the second mixture; and

(e) reacting the compound of the Formula V with a suitable sulphonylating agent *in situ* to form a sulphonate ester in the presence of a suitable base and toluene or xylene to form the compound of the Formula II.

17. A process according to claim 16, wherein the (C1-C6)alkyl-4-piperidinecarboxylate compound of the Formula III is ethyl 4-piperidinecarboxylate.

18. A process according to claims 16 or 17, wherein in step (c) the reducing agent is selected from sodium bis(2-methoxyethoxy)aluminium hydride, lithium aluminium hydride and diisobutylaluminium hydride.

19. A process according to claim 18, wherein in step (c) the reducing agent is sodium bis(2-methoxyethoxy)aluminium hydride.

20. A process according to any one or more of claims 16 to 19, wherein in step (e) the base is triethylenediamine.

(o) adding an inert organic solvent and a suitable base so as to form the free base of ZD6474;

whereafter the ZD6474 obtained in the form of the free base may be converted into a pharmaceutically acceptable salt, if necessary.

24. A process according to Claim 23 wherein step (n) is carried out in water at a temperature in the range of from 70 to 90°C.

25. A process according to claim 23 or claim 24, wherein the inert organic solvent used in step (o) is selected from tetrahydrofuran, butyronitrile and methanol.

26. A process according to any one of claims 23 to 25, wherein the base used in step (o) is selected from sodium hydroxide and potassium hydroxide.

27. A process according to any one or more of claims 23 to 26, wherein the compound of the Formula X used in step (n) is prepared according to the process according to any one or more of claims 11 to 16.

28. A process according to any one or more of claims 23 to 27, further comprising ~~further~~ purifying ZD6474 in a mixture of tetrahydrofuran, water and butyl acetate to provide the crystalline anhydrous form.